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The Western Journal of Medicine

VOLUME 163 • NUMBER 1 JULY 1995

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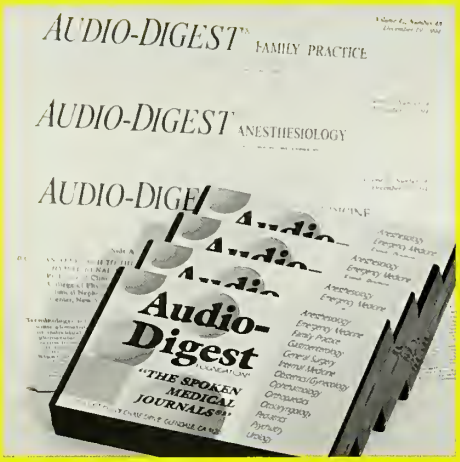

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ABSTRACTS JULY 1995

(Filley CM, Kleinschmidt-DeMasters BK: Neurobehavioral presentations of brain neoplasms. West J Med 1995; 163:19-25)

We studied 8 patients with frontal or temporolimbic neoplasms who had psychiatric presentations to clarify diagnostic criteria for distinguishing psychiatric disease from structural brain lesions and to examine brain-behavior relationships associated with cerebral neoplasms using modern neuroimaging techniques. Medical records were retrospectively reviewed for evidence of neurobehavioral and neurologic manifestations, tumor histologic features, and the results of treatment. Clinical presentations were correlated with tumor location as determined by computed tomography and magnetic resonance imaging. Patients with frontal lobe tumors presented with abulia, personality change, or depression, whereas those with temporolimbic tumors had auditory and visual hallucinations, mania, panic attacks, or amnesia. After treatment, neurobehavioral syndromes abated or resolved in 7 of 8 patients. We recommend that any patient 40 years of age or older with a change in mental state, cognitive or emotional, should have neuroimaging of the brain. Any patient with a psychiatric presentation who has specific neurobehavioral or neurologic findings or an unexpectedly poor response to psychopharmacologic treatment should also have brain imaging. These case reports extend and update observations on the importance of frontal and temporolimbic systems in the pathogenesis of neurobehavioral disorders.

NEUROLOGY
NEUROBEHAVIOR
BRAIN IMAGING
BRAIN NEOPLASMS

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The most commonly reported side effects are headache and nasal irritation, each with an incidence comparable to placebo

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(triamcinolone acetonide)

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(triamcinolone acetonide)

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Shake Well Before Using
BRIEF SUMMARY
CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.
WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.
Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with vancella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.
The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.
PRECAUTIONS
General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.
Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).
Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.
Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.
When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.
Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.
Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.
Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.
For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.
Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.
Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).
Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.
Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.
Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.
Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.
ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).
The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.
In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).
OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.
Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see product circular for full prescribing information.

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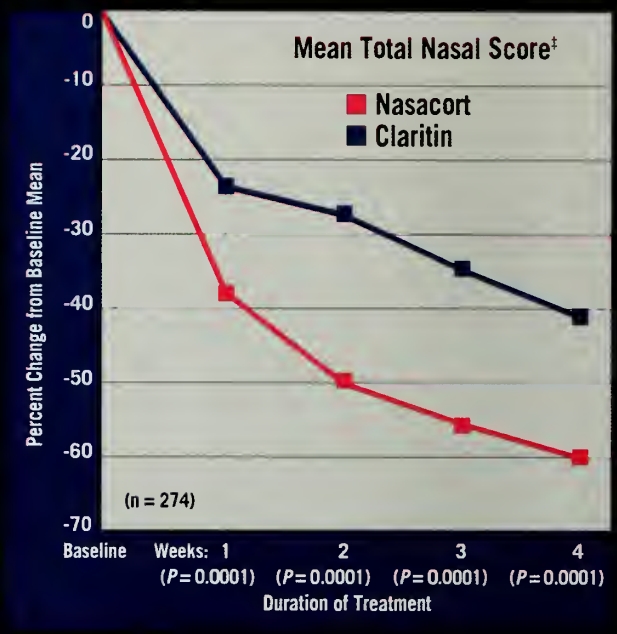
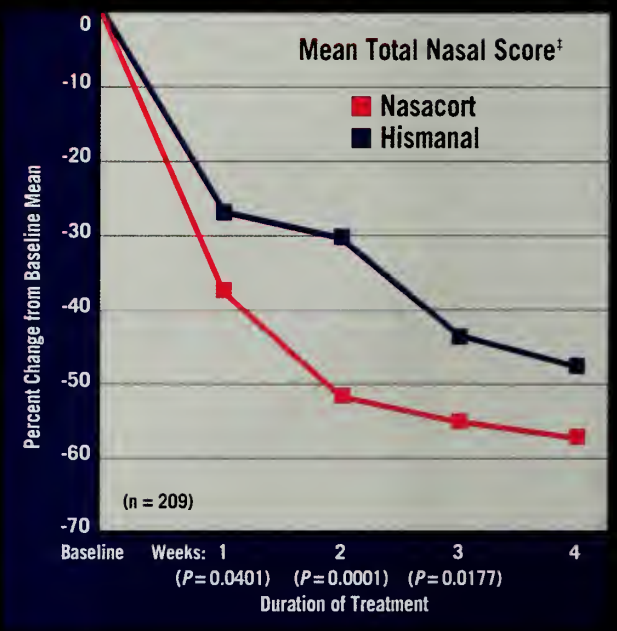


‡ Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.

NASACORT VS. HISMANAL[2†§]



** Claritin (loratadine) is a registered trademark of Schering Corporation.*
† Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).
§ Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.

REFERENCES

1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 21-22—**Clinical Update: Practical Medicine for the Primary Care Physician.** U of A and NAAHEC at Little America, Flagstaff. Fri-Sat. Contact: Rose Howe, (502) 774-6687.

October 27-28—**Ethics in Managed Care Conference.** Samaritan Health Services at the Buttes Hotel, Phoenix. Fri-Sat. Contact: Linda Luzader, (602) 495-4936.

November 2-4—**Eighth Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 5—**Career Choices.** American College of Physician Executives at the Westin La Paloma, Tucson. Sun. Contact: (800) 562-8088.

Noveber 6-10—**Physician in Management Seminar I.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 6-10—**Physician in Management Seminar II.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 12-16—**5th Annual Psychopharmacology Review**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 16—**Nurture vs. Nature: An Implication for the 21st Century.** Los Angeles Society of Allergy, Asthma and Clinical Immunology at Peninsula Hotel, Beverly Hill. Sat. 8 hrs. Contact: Diann Smith, LASAACI, P O Box 84443, Los Angeles 90073. (818) 702-0459.

September 30—**Contemporary Management of Sinusitis**. UCSF at Laurel Heights Auditorium, San Francisco. Sat. Contact: UCSF.

ANESTHESIOLOGY

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $285. Contact: CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

October 29-November 4—**Hawaiian Seminar on Clinical Anesthesia**. California Society of Anesthesiologists at Hyatt Regency Poipu Beach, Kauai, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

November 3-5—**Anesthesiology Update: 1995**. UCD at Monterey Plaza, Monterey. Fri-Sun. 12 hrs. $300. Contact: UCD.

CARDIOLOGY

August 10-12—**Critical Care Cardiology**. American College of Cardiology at Ritz-Carlton, San Francisco. Thurs-Sat. 16.5 hrs. Contact: American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

October 5-7—**Cardiology Update—1995**. UCSF at Carmel Valley Ranch Resort, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

October 19-22—**Coronary Interventions 1995.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines, San Diego. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 28—**Update in Electrocardiography and Arrhythmias**. UCSF at Ana Hotel, San Francisco. Sat. 8 hrs. $150. Contact: UCSF.

December 9—**Cardiac Therapeutics.** USC at Ritz-Carlton, Laguna Niguel. Sat. 8 hrs. $75. Contact: USC.

DERMATOLOGY

September 14-17—**3rd International Symposium on Cutaneous Fungal, Bacterial, and Viral Infection and Therapy**. UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sun. 24 hrs. $395. Contact: UCSF.

October 14-15—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. Contact: UCSF.

(Continued on Page 14)

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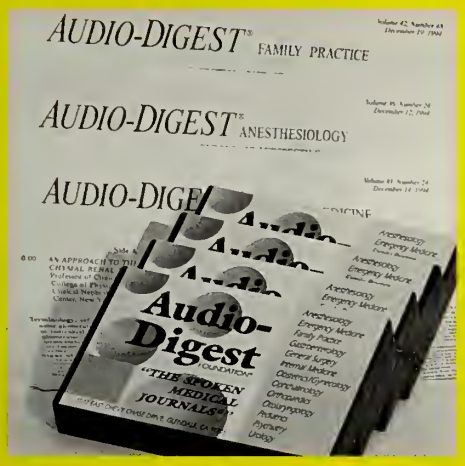

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(Continued from Page 12)

EMERGENCY MEDICINE

July 26-30—**Wilderness Medicine 1995**. American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

August 6-10—**5th National Emergency Medicine Conference: Staying Alive in '95**. Kaiser Permanente at Ritz-Carlton, Kapalua, Maui, Hawaii. Sun-Thurs. 34 hrs. Contact: Joseph Federl, Two Harrison St, #140, San Francisco 94105. (800) 782-4554.

August 23-24—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians and Emergency Physicians' Medical Group at Pan Pacific Hotel, San Diego. Wed-Thurs. 15 hrs. $295-$495. Contact: Alpen Meeting Service, (800) 451-7475.

September 22—**Advanced Burn Life Support.** Torrance Memorial Medical Center. Fri. 9 hrs. $220. Contact: Nancy Wise, Torrance Memorial Burn Center, 3330 Lomita Blvd, Torrance 90505. (310) 517-4605, ext. 7607.

October 13-15—**Advances in Emergency Medicine.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 30-November 3—**24th Annual Topics in Emergency Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

November 11-12—**Biomechanics of Trauma**. UCSD at Le Meridien Coronado. Sat-Sun. 11 hrs. $200. Contact: UCSD.

November 13-17—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 3-8—**16th Annual Current Concepts in Emergency Care**. American College of Emergency Physicians at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269.

December 11-15—**Emergency Medicine Symposium II**. UCSD at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

September 22-24—**HIV, AIDS and Women**. UCSD at La Jolla Marriott, La Jolla. Fri-Sun. 18 hrs. $175. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

August 4-6—**Cardiology for the Family Physician and Internist**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 7-9—**Dermatology for the Non-Dermatologists**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 10-23—**38th Annual Postgraduate Refresher Course-Reading Retreat, Refresher Course and Radiology Section**. USC at Maui, Hawaii. Thurs-Wed (2 wks) Contact: USC.

August 18-20—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Primary Care Medicine: A Practical Approach**. Scripps Clinic and Research Foundation at Le Meridien San Diego at Coronado. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 20-25—**Essentials of Primary Care: A Core Curriculum for Practice in the 1990s.** UCSF at Squaw Creek Resort, North Lake Tahoe. Sun-Fri. 25 hrs. $545. Contact: UCSF.

August 21-23—**Sports Medicine and Occupational Medicine for Primary Care Physicians**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 28-31—**Current Concepts in Primary Care Cardiology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Mon-Thurs. 18 hrs. $385. Contact: UCD.

September 9—**Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Mariott, Mission Valley, San Diego. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

September 22-23—**Musculoskeletal Problems in Primary Care**. UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sat. 12.5 hrs. Contact: UCSF.

October 11-13—**10th Annual Primary Care Medicine: Principles and Practice.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 20 hrs. $495. Contact: UCSF.

October 14— **Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Radisson Hotel, Sacramento. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

October 16-18—**Neurology and Outpatient Psychiatry for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

xOctober 25-28—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

October 26-29—**Nevada Academy of Family Physicians.** NAFP at Tropicana Hotel, Las Vegas, Nevada. Thurs-Sun. 21 hrs. Contact: Barbara Bollin, NAFP, P O Box 27713, Las Vegas, NV, 89126-1713. (702) 647-0117.

November 6-8—**Geriatrics Update 1995**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 563-4800.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (714) 824-5926.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-6774.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 342-1544.

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INFECTIOUS DISEASE

November 3-5—**Advances in Infectious Disease**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

September 29-October 1—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 16.5 hrs. $430. Contact: UCSF.

August 20-25—**Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $475. Contact: UCD.

NEPHROLOGY

September 16—**35th Annual Scientific Symposium on Kidney Disease**. National Kidney Foundation of Southern California at Sheraton Universal City. Sat. 6.5 hrs. Contact: Johanna Goldberg, (310) 641-8152.

November 9-10—**International Symposium on Continuous Renal Replacement Therapy.** UCSD. Thurs-Fri. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

October 15—**OB/GYN Pathology**. USC at Red Lion Hotel, Glendale. Sun. 6 hrs. $175. Contact: USC.

October 16-20—**OB/GYN Review**. USC at Red Lion Hotel, Glendale. Mon-Fri. 38 hrs. $640. Contact: USC.

December 7-10—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's, Las Vegas. Thurs-Sun. $295. Contact: Center for Continuing Medical Education, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OCCUPATIONAL/ENVIRONMENTAL

July 31-August 1—**8th Annual Occupational Safety and Health Institute.** Long Beach Regional Medical Education Center and University of California Berkeley Center for Occupational and Environmental Health at San Francisco Airport Hilton. Mon-Tues. Contact: COEH, (510) 231-5645.

October 23-27—**Occupational and Environmental Medicine V**. UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

ONCOLOGY

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

September 16—**Benign Essential Blepharospasm**. UCD at Red Lion Hotel, Sacramento. Sat. 6 hrs. $125. Contact: UCD.

ORTHOPEDICS

July 29-August 5—**Update in Orthopedics '95**. Kaiser Permanente Medical Center South San Francisco at Hyatt Regency, Kauai, Hawaii. Sat (1 wk). 18 hrs. $499. Contact: Jerry VanMeter, MD, 1200 El Camino Real, S San Francisco 94080. (415) 742-2461.

November 9-11—**Integrated Function of the Lumbar Spine and Sacroiliac Joints.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 15 hrs. $335. Contact: UCSD.

OTOLARYNGOLOGY

September 10-15, October 15-20—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 2-4—**San Francisco Otology-Neurotology—1995**. UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 22 hrs. $425. Contact: UCSF.

PATHOLOGY

August 12-19—**16th Annual Comprehensive Fine Needle Biopsy Course**. UCSF at Ritz-Carlton, San Francisco. 1 wk. 27 hrs. $950. Contact: UCSF.

November 10-11—**Pathophysiology and Treatment of Gastroesophageal Reflux.** USC at at Health Sciences Campus. Fri-Sat. 16 hrs. Contact: USC.

PEDIATRICS

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

July 25-29—**Neuropsychiatric Emergencies-Crisis.** American Academy of Family Physicians with Southern California Neuropsychiatric Institute at Hapuna Prince Beach Hotel, Kamuela, Hawaii. Tues-Sat. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

November 3-5—**41st Annual Group Therapy Symposium**. UCSF. Fri-Sun. Contact: UCSF.

PULMONARY/CRITICAL CARE

October 19-21—**14th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 17 hrs. $430. Contact: UCSF.

RADIOLOGY

September 30-October 1—**7th Annual Ultrasound Update 1995.** UCD at Red Lion Hotel, Sacramento. Sat-Sun. 10 hrs. $235. Contact: UCD.

October 21-22—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. 13 hrs. $375. Contact: UCSD.

October 23-27—**20th Annual San Diego Postgraduate Radiology Course**. UCSD at Hotel del Coronado. Mon-Fri. 27 hrs. $575. Contact: UCSD.

October 27-28—**15th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado. Fri-Sat. 14 hrs. $375. Contact: UCSD.

SURGERY

November 11-14—**Surgical Advances in Cleft and Cleft Palate.** UCD at Monterey Plaza, Monterey. Sat-Tues. 18 hrs. $450. Contact: UCD.

December 1-3—**International Symposium on TMJ Arthroscopy and Arthroscopic Surgery**. Fri-Sun. $695. Contact: Peg Hoelderlin, c/o Professional Image, (714) 760-1522.

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August 28-September 1—**Medical Informatics Introductory Short Course.** Stanford University's Center for Advanced Medical Informatics at Stanford. Mon-Fri. 34.25 hrs. $900-$1300. Contact: Irene Zagazeta, (415) 723-6979.

September 14-15—**4th Regional Symposium on the Design and Methods of Clinical Trials.** UCSF at San Francisco. Thurs-Fri. 12.5 hrs. $350. Contact: UCSF

September 30—**Outcomes: More Than a Buzzword—A Symposium on Outcomes Studies for Health Care Professionals**. FHP Healthcare at Anaheim Hilton and Towers. Sat. 6 hrs. $65. Contact: Tina Pirzadeh, (714) 378-5780..

October 7—**Multi-Cultural Diversity in Health Care Symposium**. UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

December 23-29—**Advances in Medicine 1995**. Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Fri. 6 hrs. $475. Contact: Symposium Maui, PO Box 10185, Lahaina, HI 96761. (808) 661-8032.

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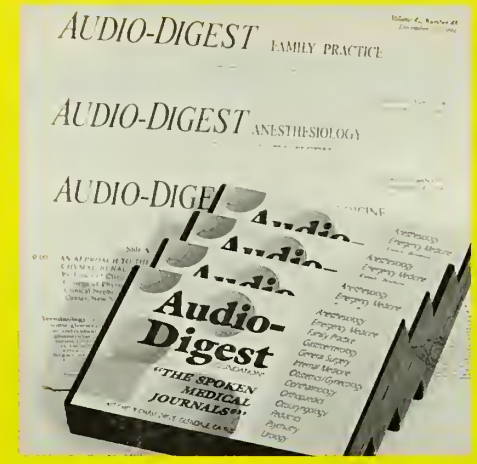

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Articles

Neurobehavioral Presentations of Brain Neoplasms

CHRISTOPHER M. FILLEY, MD, *and* BETTE K. KLEINSCHMIDT-DeMASTERS, MD, *Denver, Colorado*

We studied 8 patients with frontal or temporolimbic neoplasms who had psychiatric presentations to clarify diagnostic criteria for distinguishing psychiatric disease from structural brain lesions and to examine brain-behavior relationships associated with cerebral neoplasms using modern neuroimaging techniques. Medical records were retrospectively reviewed for evidence of neurobehavioral and neurologic manifestations, tumor histologic features, and the results of treatment. Clinical presentations were correlated with tumor location as determined by computed tomography and magnetic resonance imaging. Patients with frontal lobe tumors presented with abulia, personality change, or depression, whereas those with temporolimbic tumors had auditory and visual hallucinations, mania, panic attacks, or amnesia. After treatment, neurobehavioral syndromes abated or resolved in 7 of 8 patients. We recommend that any patient 40 years of age or older with a change in mental state, cognitive or emotional, should have neuroimaging of the brain. Any patient with a psychiatric presentation who has specific neurobehavioral or neurologic findings or an unexpectedly poor response to psychopharmacologic treatment should also have brain imaging. These case reports extend and update observations on the importance of frontal and temporolimbic systems in the pathogenesis of neurobehavioral disorders.

(Filley CM, Kleinschmidt-DeMasters BK: Neurobehavioral presentations of brain neoplasms. West J Med 1995; 163:19-25)

Whereas patients with brain neoplasms characteristically have focal neurologic disturbances, it was well recognized before neuroimaging became available that some tumors manifest with neurobehavioral or psychiatric features.[1-7] Conversely, only a small percentage (3%) of institutionalized psychiatric patients have intracranial tumors.[8,9] Because the number of psychiatric patients who have brain tumors is relatively small, it is a matter of debate among psychiatrists and neurologists whether all patients with newly recognized psychiatric symptoms should undergo neuroimaging studies. This issue was reviewed with regard to computed tomography (CT) a decade ago.[10] Since then, magnetic resonance imaging (MRI) has become widely available, and little information has appeared on the utility of MRI in this setting. Nevertheless, most clinicians advocate CT or MRI scanning in older patients with a new occurrence of neurobehavioral symptoms or signs and patients of any age who have these features accompanied by headache, nausea and vomiting, papilledema, seizures, or focal deficits.

Despite this general consensus, patients with brain tumors may still mistakenly carry a diagnosis of primary psychiatric disorder months or years before the discovery of tumor. Since 1987 we have seen eight patients at our institution with frontal or temporolimbic tumors who had psychiatric symptoms for months or years before thorough evaluations detected brain neoplasms. All patients with low-grade, benign, or excisable neoplasms (7 of 8) were substantially improved or cured after surgical treatment, emphasizing the importance of a correct diagnosis. Modern detailed neuroimaging studies allow a useful correlation between tumor location and clinical presentation. These cases are of interest in light of recent advances in the understanding of brain-behavior relationships.

Method

This was a retrospective study of patients seen at our institution since 1987 who had psychiatric presentations that were later attributed to a brain neoplasm. Cases were identified after brain tissue specimens were submitted for neuropathologic diagnosis. One of us reviewed all patients' medical records in detail (C.M.F.) or determined their tumor histology (B.K.K.). All CT and MRI scans were reviewed, and tumor locations were correlated with clinical presentations.

From the Departments of Neurology (Dr Filley) and Pathology and Psychiatry (Dr Kleinschmidt-DeMasters), University of Colorado Health Sciences Center (UCHSC) and the Denver Veterans Affairs Medical Center, Denver.
Reprint requests to Christopher M. Filley, MD, Behavioral Neurology Section, UCHSC B183, 4200 E Ninth Ave, Denver, CO 80262-0813.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CT = computed tomography
MRI = magnetic resonance imaging
PET = positron emission tomography

Report of Cases

Patient 1. This 56-year-old right-handed homemaker had progressive apathy, social withdrawal, and poor self-care for three years and was admitted to a psychiatric facility for depression. Because she was unresponsive to appropriate antidepressant medications, a CT scan was taken of the head. This study revealed an enhancing, 8-cm, medial bifrontal mass (Figure 1). Total excision of a benign transitional-type meningioma led to rapid and dramatic improvement, and four months after the operation she was animated, cheerful, and motivated to resume her previous life.

Patient 2. This 63-year-old left-handed taxi driver sought care because for five weeks, in a departure from his previous personality, he had been apathetic and irritable and two weeks before admission right hemiparesis and anomia had developed. A CT scan disclosed a 3 × 4 cm enhancing lesion involving the left medial frontal lobe, the genu of the corpus callosum, and the right medial frontal lobe (Figure 2). Small stereotactic biopsies revealed a malignant small-cell neoplasm that could not be further characterized by immunohistochemistry studies, and treatment with cranial irradiation and carmustine (formerly BCNU) was instituted. Two months after discharge, his personality change had resolved considerably, and a CT scan showed dramatic resolution of the mass lesion after therapy, most consistent with a primary malignant lymphoma of the central nervous system (CNS). He died ten months later of respiratory distress and sepsis, and an unsuspected adenocarcinoma of the cecum was found. The brain showed multifocal, ill-defined infiltrates of malignant immunoblastic lymphoma around blood vessels and in periventricular and leptomeningeal sites.

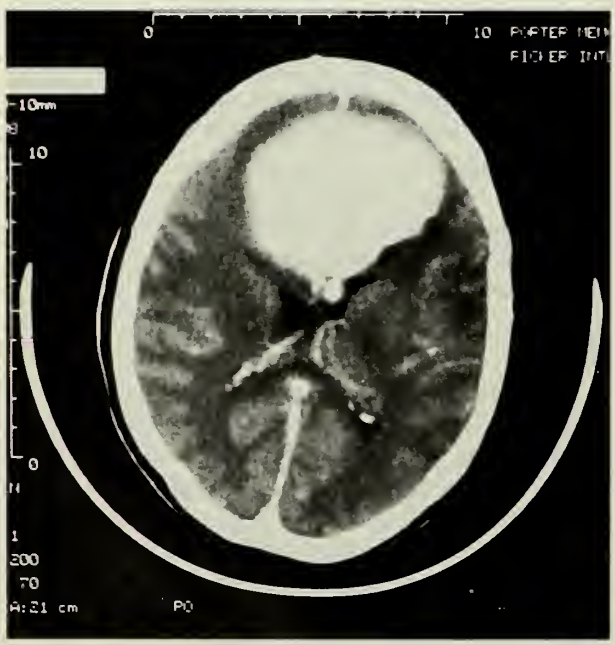

Figure 1.—*Frontal lobe tumor.* Patient 1 had abulia due to a benign meningioma. A computed tomographic scan shows severe compromise of both medial frontal lobes. Note the homogeneous enhancement in the 8-cm mass.

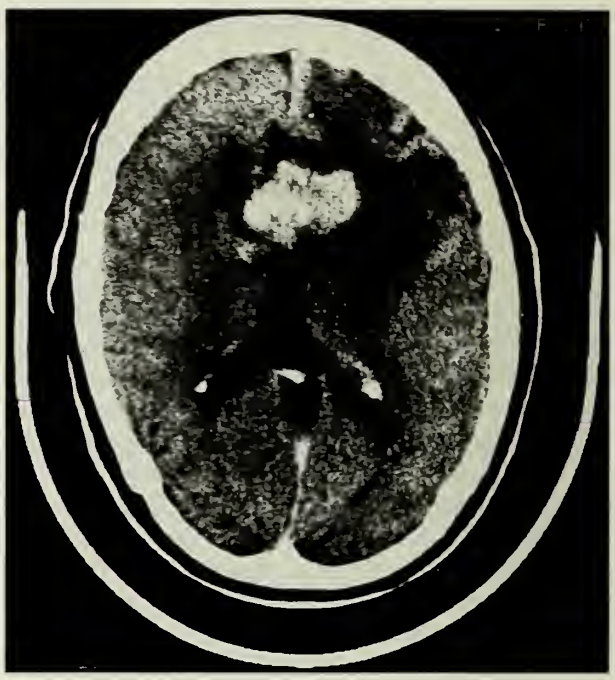

Figure 2.—*Frontal lobe tumor.* Patient 2 presented with personality change from his lymphoma that involved both medial frontal lobes and crossed the corpus callosum, as seen on this enhanced computed tomographic scan. Extensive low-density edema surrounds the tumor.

Patient 3. This 53-year-old left-handed postal worker for the past 18 months had had profound depression and a 27-kg (60-lb) weight loss before left hemiparesis was noted. A T1-weighted MRI scan showed a 3-cm enhancing mass lesion in the anterior right frontal lobe (Figure 3). Further evaluation revealed a mass in the left lower lobe of the lung, and excision of the brain tumor led to a diagnosis of moderately differentiated, metastatic squamous cell carcinoma. After the operation, the patient reported substantial lessening of his depressive symptoms and only mild residual hemiparesis.

Patient 4. After two months of auditory hallucinations, this 22-year-old right-handed mechanic was admitted to a psychiatric hospital. Memory and word-finding problems were then noted, and he was found on CT and T2-weighted MRI to have a 2-cm, nonenhancing, left medial temporal mass (Figure 4). Total excision of this lesion, which required two procedures, showed it to be a low-grade oligoastrocytoma, grade 1 of 4. Although he had been treated with haloperidol for hallucinations, tumor resection led to lessening of his symp-

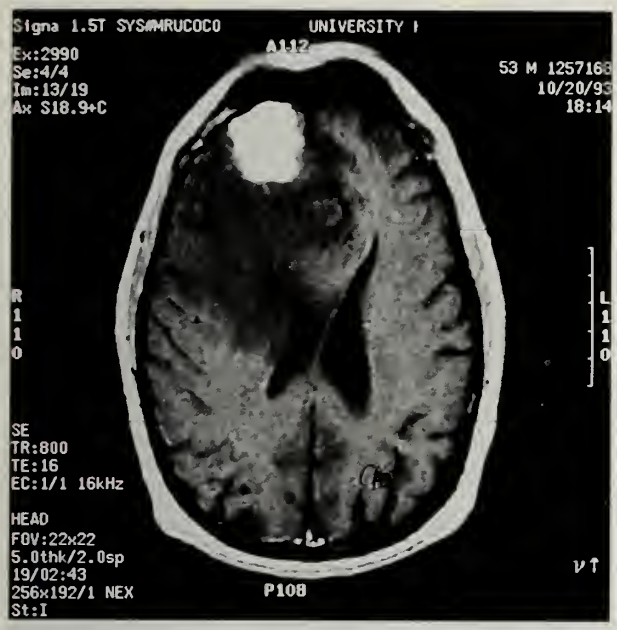

Figure 3.—*Frontal lobe tumor.* Patient 3 was profoundly depressed preoperatively, but after surgical removal of his enhancing 3-cm right frontal pole metastasis, he was greatly improved. The large area of surrounding edema on this enhanced T1-weighted magnetic resonance imaging scan further compromised the right frontal lobe and added to his neurobehavioral deficit (TR = 800 msec, TE = 16 msec).

toms, and the drug was no longer required. Follow-up at two years revealed no hallucinations and no tumor recurrence.

Patient 5. This 31-year-old right-handed laborer was admitted to a psychiatric hospital with auditory and visual hallucinations. The neurologic examination disclosed left hemiparesis, and neuroimaging studies (CT, MRI, and angiography) revealed a 6-cm tumor in the right temporal lobe, with massive edema extending into the frontal and parietal lobes (Figure 5). Surgical excision showed the lesion to be an oligodendroglioma, grade 2 of 4. The patient subsequently showed improvement in his psychosis, but had recurrence of the tumor, necessitating reoperation. After several debulking procedures, he eventually died; no autopsy was performed.

Patient 6. After a 20-year history of intermittent depression, this 56-year-old right-handed homemaker had a new onset of disorganized thinking, flight of ideas, and pressured speech three months before admission to a psychiatric hospital for mania. An MRI scan revealed a butterfly lesion involving 3-cm masses in both temporal lobes and tumor in the corpus callosum and the fornix (Figure 6). Biopsy disclosed a glioblastoma multiforme. Three weeks later, she had a perforated duodenal ulcer necessitating emergent surgical intervention and a Billroth II procedure, then lapsed into stupor and coma, dying a month after the initial diagnosis. An autopsy showed a large subdiaphragmatic abscess from duodenal perforation and amyloid deposits in the spleen and adrenal glands, with a normal bone marrow. The glioblastoma multiforme infiltrated the limbic system, including the left hippocampus and amygdala, the hypothalamus, the fornices, and the right hippocampus and amygdala. The posterior thalami, septum pellucidum, and deep right parietal lobe were also involved.

Patient 7. Two months after the onset of panic attacks, characterized by episodic fear, dyspnea, lower extremity paresthesias, diaphoresis, and tremulousness, this 56-year-old right-handed farmer was found on MRI scan to have a 5 × 4 cm pituitary mass extending into the left medial temporal lobe and thalamus; in addition, the lesion compressed the right medial temporal lobe (Figure 7). The patient underwent two procedures to reduce this weak gonadotropic cell pituitary adenoma to 10% of its original size, with a greater debulking of the tumor on the right side and more decompression of the right than the left temporal lobe. After the second operation, his panic attacks completely resolved.

Patient 8. This 45-year-old right-handed secretary had dysfunction of her recent memory for 12 months before admission. The family noted apathy and poor motivation, and she was seen by a psychiatrist who diagnosed depression. Neurologic examination, however, disclosed amnesia and a subtle bitemporal hemianopia, prompting an MRI scan. A 6 × 3 × 3 cm suprasellar mass was found that extended upward into the thalami and displaced the forniceal columns (Figure 8). After two transsphenoidal procedures that resulted in partial resection of this weak gonadotropic cell pituitary adenoma, her memory improved substantially.

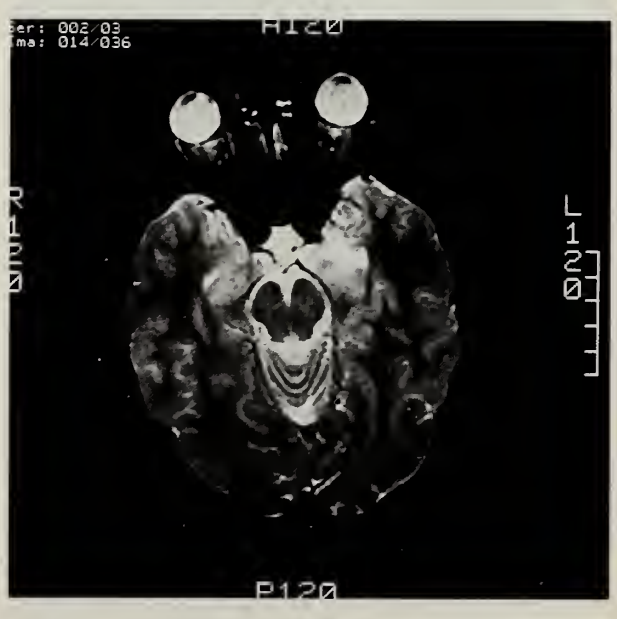

Figure 4.—*Temporolimbic tumor.* Patient 4 had auditory hallucinations for 2 months before the removal of a low-grade left temporal lobe oligoastrocytoma. The small 2-cm lesion shows increased signal intensity on this T2-weighted magnetic resonance imaging scan (TR = 2.0 sec, TE = 80 msec).

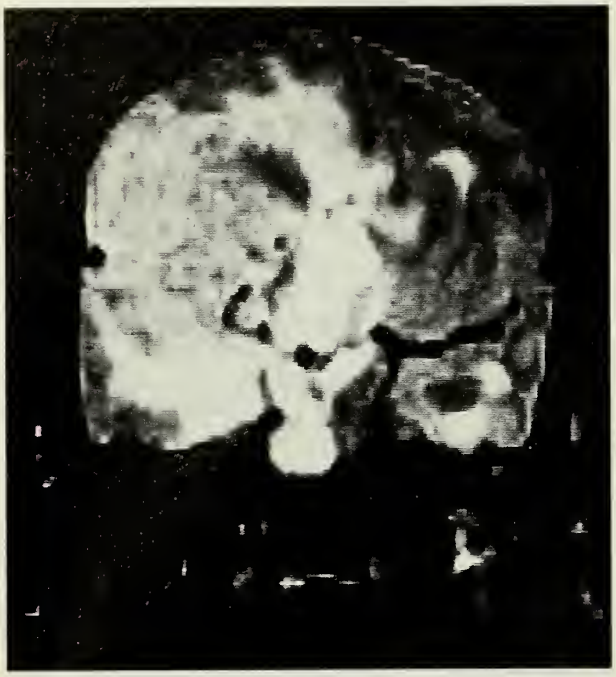

Figure 5.—*Temporolimbic tumor.* Patient 5 had auditory and visual hallucinations from presumed primary psychiatric disease for an indefinite length of time before being studied radiologically. This T2-weighted coronal magnetic resonance imaging scan, hampered by movement artifact, shows the massive right temporolimbic oligodendroglioma with additional high signal intensity in the frontoparietal areas thought to represent edema (TR = 3.0 sec, TE = 40 msec).

Summary of Cases

These eight cases represent a broad spectrum of intracranial neoplasms: one glioblastoma multiforme, one primary CNS malignant immunoblastic lymphoma, one oligoastrocytoma, one oligodendroglioma, one meningioma, two pituitary adenomas, and one metastatic lung carcinoma. Although the type of neoplasm varied, each was primarily located in frontal or temporolimbic areas. All the patients presented with symptoms and signs of neurobehavioral involvement that led to the consideration of primary psychiatric disorders (Table 1). Detailed neuropsychological testing had not been done preoperatively on any patient.

All patients with low-grade, benign, or excisable neoplasms were greatly improved or cured after surgical intervention and tumor resection (patients 1, 3, 4, 7, 8). One patient with a glioblastoma multiforme (patient 6) died rapidly, and one with primary CNS lymphoma improved temporarily with intensive irradiation, chemotherapy, and lesion reduction but died ten months later of systemic causes (patient 2). The oligodendroglioma of patient 5 was far advanced by the time a correct diagnosis was obtained, although surgical debulking did effect considerable clinical improvement.

These cases all suggest that the neoplasm was the actual cause of the neurobehavioral dysfunction. Table 1 divides the cases into those with frontal and those with

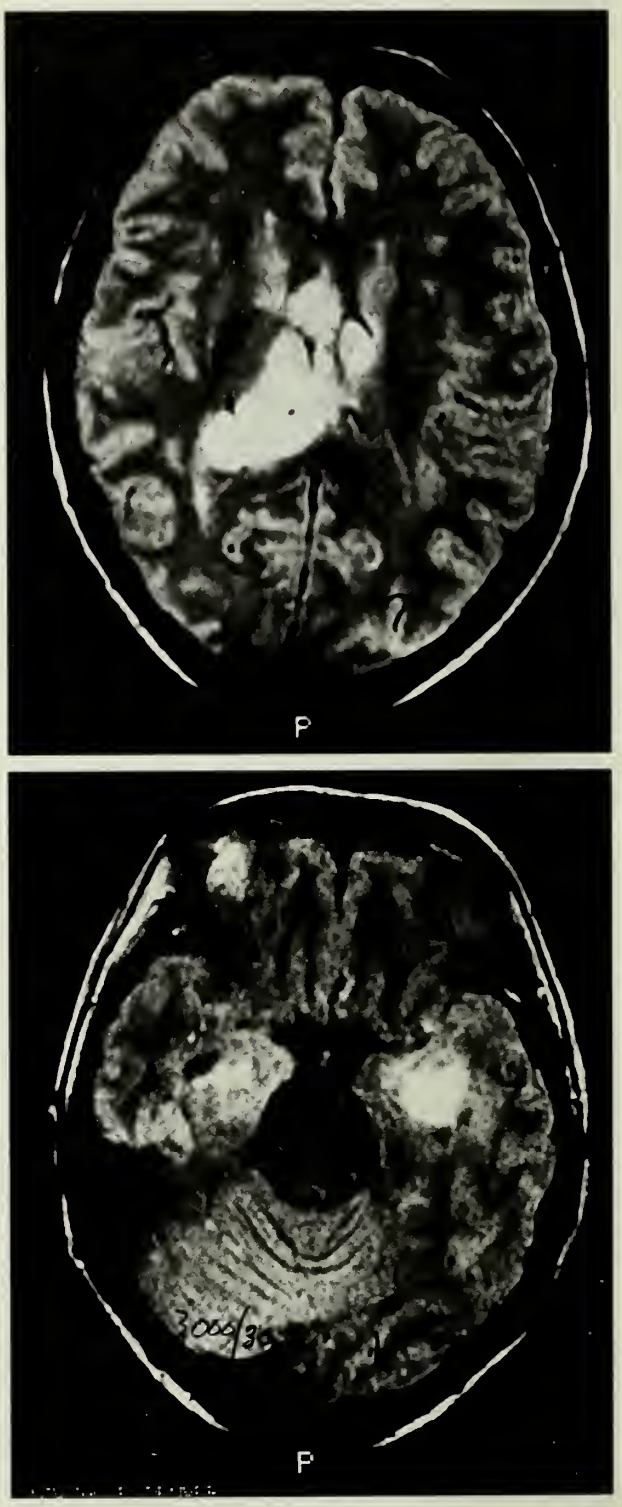

Figure 6.—*Temporolimbic tumor.* Patient 6 was manic for 3 months, and her age prompted this first echo T2-weighted magnetic resonance imaging scan showing bilateral medial temporal involvement with glioblastoma multiforme (TR = 3.0 sec, TE = 30 msec). **Top,** The tumor is shown in the forniceal columns and right posterior temporal lobe. **Bottom,** More left-sided anterior temporal lobe involvement is shown. The patient died soon thereafter, and autopsy revealed diffuse infiltration of the temporal lobes, forniceal columns, thalami, and hypothalami by glioblastoma multiforme.

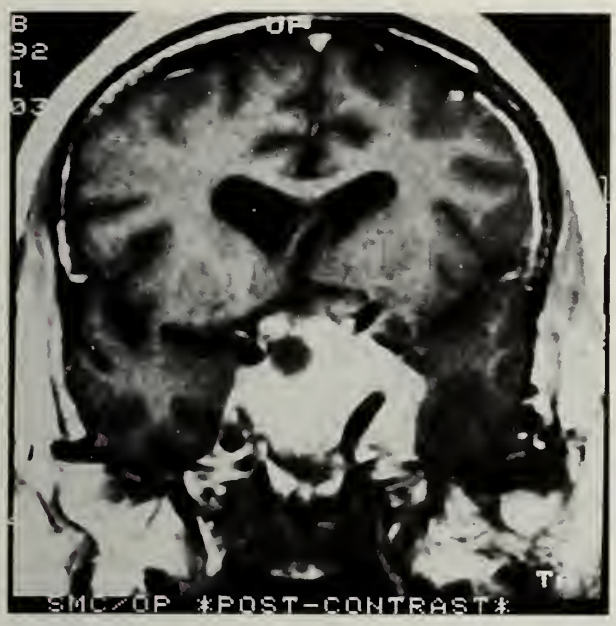

Figure 7.—*Temporolimbic tumor.* Patient 7 had 2 months of panic attacks, and this T1-weighted, enhanced coronal magnetic resonance image shows a pituitary macroadenoma extending into the left temporal lobe and thalamus and compressing the right medial temporal lobe (TR = 45 msec, TE = 15 msec). Debulking eliminated the panic attacks.

temporolimbic sites of origin, and all the presentations in both groups can be associated with damage or dysfunction in the specific areas involved. Although psychiatric diagnoses were considered in all patients, careful attention to neurobehavioral and neurologic aspects of these cases resulted in accurate diagnoses and appropriate therapy.

Discussion

Diagnostic Considerations

Classic neurologic symptoms and signs may be minimal or absent in patients with brain neoplasms, and even large tumors, because of a slow growth rate, may escape detection. Medial frontal lobe or periventricular midline nonobstructive tumors may also present with subtle, nonfocal abnormalities. Before CT and MRI scanning were available, many such cases in psychiatric settings were undiagnosed,[8] and it seems probable that some still go undetected. With the availability of CT and particularly MRI, however, the likelihood of finding tumors is much greater, and the cost of neuroimaging procedures is outweighed by the possibility of failing to detect surgically accessible lesions. Benign tumors such as meningiomas and pituitary adenomas may be curable by surgical therapy alone.

Patients with psychiatric presentations usually have psychiatric disorders, but the possibility of a neurobehavioral syndrome due to a structural lesion should be considered. Brain tumors can be suspected in particular because of their typically insidious onset, and they often present with recognizable neurobehavioral dysfunction. Although formal mental state examination is crucial, the distinction of patients with neoplastic brain lesions from those with primary psychiatric illnesses can be problematic. Psychiatrists and neurologists well recognize that brain tumors cannot always be detected by attention to neurobehavioral features. Nevertheless, detailed mental state testing combined with the traditional neurologic examination will clearly uncover more cases of these potentially reversible lesions. Neuropsychological assessment can also contribute useful information.

The question of which patients should undergo a brain imaging study is pertinent.[10] Although such testing is of possible interest in all patients with a change in behavior, cost limitations are a reality, and some clinical guidelines are helpful. We recommend that any patient 40 years of age or older with an unequivocal change in neurobehavioral status, cognitive or emotional, should have a CT or MRI scan of the brain (Table 2). Applying this criterion clearly led to the detection of neoplasms in patients 2, 3, 7, and 8. Patient 6, with a 20-year history of depression but a new onset of mania at age 56, also illustrates this point. Primary psychiatric disorders such as schizophrenia and bipolar disorder typically begin in adolescence or young adulthood,[11] and the decision to scan the brain of a person younger than 40 can be made on an individual basis. The presence of symptoms and signs such as headache, nausea and vomiting, papilledema, seizures, and focal deficits clearly helps in this regard (Table 2). In our series, most patients were older than 40, and the two younger ones who might have had

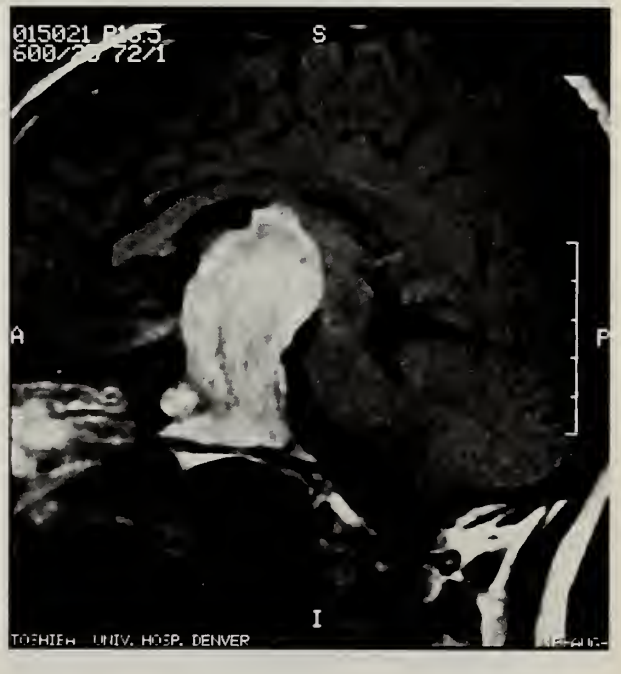

Figure 8.—*Temporolimbic tumor.* Patient 8 was amnesic for a year before this T1-weighted, enhanced sagittal magnetic resonance imaging scan disclosed a pituitary macroadenoma that upwardly displaced the forniceal columns and thalami (TR = 600 msec, TE = 25 msec). Debulking yielded substantial improvement in her memory.

schizophrenia (patients 4 and 5) had neurobehavioral or neurologic features (amnesia, anomia, hemiparesis) that distinguished them from patients with primary psychiatric illness. Another feature that implies the need for scanning is unresponsiveness to appropriate pharmacologic treatment of presumed psychiatric illness, as was the case in patient 1.

Clinical-Anatomic Correlations

Any lesion that destroys or disturbs a region of the brain can be expected to have an effect on a person's functioning, be it motor, sensory, or neurobehavioral. Neoplasms, however, pose some difficulties for examining clinical-anatomic correlations. Unlike cerebrovascular lesions, neoplasms may not be confined to discrete areas of the brain, and therefore, a precise correlation of lesion location and behavioral change is often not possible. Particularly with infiltrating gliomas, the possibility of associated edema, mass effect, and hydrocephalus and the progressive growth of the neoplasm can complicate these clinical-anatomic relationships. Neurobehavioral features and focal neurologic deficits can, however, be helpful in localizing the site of the neoplasm. Moreover, the introduction of CT and especially the more sensitive MRI has greatly improved the localization of brain tumors and permitted better clinical-anatomic correlation.

All eight cases presented with clinical features suggesting psychiatric dysfunction. Neuropsychiatric disturbances are more frequently associated with frontal and temporolimbic lesions and rarely with tumors in the parietal or occipital lobes.[4,7,12] The frontal lobes are the largest and phylogenetically most recent lobes of the human brain, and they play a central role in the organization and integration of behavior.[13] Three types of "frontal lobe syndrome" are recognized, based on the precise location of frontal lobe lesions: a dorsolateral syndrome that produces deficits in the organization and planning of behavior (executive function), an orbitofrontal syndrome with prominent disinhibition, and a medial-frontal syndrome with apathy or abulia.[14] All of these changes are more dramatic with bilateral than with unilateral frontal lobe involvement. In practice, these profiles often merge due to the widespread nature of many frontal lobe tumors. Patients 1 and 2 showed neurobehavioral changes consistent with bilateral medial-frontal involvement. Patient 3 had depression, another syndrome associated with frontal lobe damage.[14]

TABLE 1.—*Neurobehavioral Correlates of Neoplasm Location*

Patient	Tumor	Location	Presentation
		Frontal Lobe Tumors	
1	Meningioma, transitional subtype	Bilateral medial frontal lobe	Abulia
2	Malignant primary immunoblastic lymphoma	Bilateral medial frontal lobe	Personality change
3	Metastatic squamous cell carcinoma of lung	Right frontal lobe	Depression
		Temporolimbic Tumors	
4	Oligoastrocytoma, grade I of IV	Left temporal lobe	Auditory hallucinations
5	Oligodendroglioma, grade II of IV	Right temporal lobe with massive edema	Auditory and visual hallucinations
6	Glioblastoma multiforme	Massive bilateral temporolimbic involvement	Mania
7	Pituitary adenoma, weakly gonadotrophic	Left temporal lobe with pressure on right parahippocampal gyrus	Panic attacks
8	Pituitary adenoma, weakly gonadotrophic	Thalami with displacement of forniceal columns	Amnesia

TABLE 2.—*Indications for Neuroradiologic Evaluation of Patients With Psychiatric Presentations*

Age ≥ 40 yr	Any new onset of cognitive or emotional dysfunction Unresponsiveness to appropriate drug treatment of presumed psychiatric disease
Comment: MRI and CT are roughly equivalent in detecting metastases, high-grade gliomas, and meningiomas that are common in this older age group; CT is particularly indicated when cost, facility access, pacemaker, cranial metal, agitation, claustraphobia, or back or arthritis pains preclude MRI scanning	
Age < 40 yr	Any new onset of cognitive or emotional dysfunction if associated with headache, nausea and vomiting, papilledema, seizures, or focal deficits Unresponsiveness to appropriate drug treatment of presumed psychiatric disease
Comment: MRI is preferable to CT because it more accurately detects low-grade astracytomas and oligodendrogliomas, which tend to occur in this age group	

CT = computed tomography, MRI = magnetic resonance imaging

Temporolimbic tumors tend to cause psychosis due to the disruption of limbic system structures,[1,2,4,12] including components of the Papez circuit: the hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nucleus, cingulate gyrus, and parahippocampal gyrus.[15] As is true of frontal lobe lesions, bilateral temporolimbic damage is more likely to cause these clinical manifestations.[16] In younger patients, neuropsychiatric manifestations are commonly due to primary psychiatric diseases, and those with brain tumors need, in particular, to be distinguished from patients with schizophrenia. Recent research has suggested a distinction between two varieties of schizophrenia; one with prominently "negative" features of apathy and social withdrawal, and the other with "positive" features such as delusions and hallucinations.[17] Positron emission tomography (PET) studies have shown decreased metabolic activity in the frontal lobes of schizophrenic patients with negative features,[17] and left temporal cortical volume loss has recently been demonstrated using quantitative MRI in patients with schizophrenia with positive features.[18] Whereas patients 1, 2, and 3 had presentations similar to those of schizophrenia with nega-

tive features, patients 4 and 5, with their prominent hallucinations, closely resembled those with schizophrenia with positive features. One of the most important distinctions between brain tumors and schizophrenia, however, is age. Schizophrenia rarely begins after age 40, and most schizophrenic patients are first seen between the ages of 15 and 25. In contrast, a new onset of primary or metastatic brain tumors is uncommon in this age range.

Mania is a disorder of mood and affect also associated with temporal lobe lesions, often right-sided.[19] Patient 6 had a unipolar depression without mania for many years, and the abrupt onset of her mania was more likely due to the bitemporal neoplasm than to a bipolar psychiatric disorder. Because of the extensive size and malignancy of her tumor, the prognosis was poor.

Panic attacks were initially noted in patient 7, who had a left temporal lobe lesion compressing the right medial temporal lobe. The right parahippocampal gyrus is a region recently implicated in panic attacks by PET studies.[20] Although another case of a pituitary adenoma causing panic attacks has been reported in the literature,[21] this case also had contributing factors from endocrinologic disturbance associated with Cushing's disease, and no compression of the parahippocampal gyrus was present. Patient 7 had a gonadotropic cell adenoma, and the panic attacks were most likely due to structural rather than endocrinologic abnormalities. A structural cause is supported by the fact that the panic attacks resolved after the tumor was debulked.

Memory loss was prominent in patient 8, emphasizing that amnesia is strongly associated with lesions of the temporolimbic regions, particularly the hippocampus and its connections.[22] Endocrinologic disturbances associated with this gonadotropic cell pituitary adenoma were not thought to be contributory. In this case, the thalamic involvement and displacement of the forniceal columns by the large midline pituitary adenoma likely caused the amnesia, which improved after surgical therapy.

Conclusion

In summary, we report the cases of eight patients with frontal or temporolimbic tumors who presented psychiatrically but whose age of onset, associated features, or unresponsiveness to appropriate pharmacologic therapy suggested a structural lesion. We advocate brain imaging in patients 40 years of age or older who have the onset of cognitive or emotional dysfunction and in any patient with such a presentation who has additional neurobehavioral or neurologic features or a poor response to appropriate psychopharmacologic treatment. This series of cases highlights the importance of searching for possibly curable neoplasms that might otherwise go undetected. These cases also emphasize the importance of frontal and temporolimbic systems in the pathogenesis of neurobehavioral disorders.

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Articles

Total Knee Replacement
A Guideline to Reduce Postoperative Length of Stay

SCOTT R. WEINGARTEN, MD, MPH; LAURA CONNER, RN; MARY RIEDINGER, RN, MSN; ANTHONY ALTER, MD; WILLIAM BRIEN, MD; *and* A. GRAY ELLRODT, MD, *Los Angeles, California*

In a retrospective study in an academic, acute-care community hospital, we studied the possible safety and effectiveness of a practice guideline recommending early discharge from the hospital for patients having uncomplicated total knee replacement. Of 206 patients receiving knee replacements, 162 (79%) were classified by the guideline as being at low risk for complications between the 4th and 7th postoperative days. Use of the guideline could have reduced the postoperative length of stay from 7.3 ± 2.6 days to 4 days for the 112 patients (54%) who became low risk on the 4th postoperative day. Explicit and implicit review of the quality of care determined that 157 patients (96.9%; 95% confidence interval, 92.9%, 99.0%) could have been safely transferred from the acute-care hospital to an appropriate setting when they became classified at low risk between the 4th and 7th postoperative days. Clinical practice guidelines can possibly be used to reduce the postoperative length of acute-care hospital stay for patients having knee replacements. This guideline requires further study in a controlled clinical trial before it can be recommended for use.

(Weingarten SR, Conner L, Riedinger M, Alter A, Brien W, Ellrodt AG: Total knee replacement—A guideline to reduce postoperative length of stay. West J Med 1995; 163:26-30)

About 125,000 knee replacement operations are done annually in the United States at a cost of more than $3 billion per year.[1,2] Even though the frequency of knee replacement exceeds that of hip replacement,[1] little is known about the cost-effectiveness of the care of these patients after the operation. Previous studies of common medical conditions have shown relatively safe ways to shorten lengths of hospital stay and reduce hospital costs.[3-6] Patients undergoing knee replacements may achieve similar benefits.

Practice guidelines and clinical pathways to enhance safe and effective care for hospitalized patients with common conditions are being developed.[7-11] Valid and reliable clinical data are essential in this effort, but are often lacking.[7] The American Academy of Orthopaedic Surgeons' discharge guidelines for patients receiving total knee arthroplasty do not have recommendations about the medically or surgically appropriate length of hospital stay.[12]

We retrospectively studied a clinically derived practice guideline that prescribed the appropriate length of stay in an acute-care hospital for patients undergoing knee replacement operations. In a hypothetical experiment, we determined the possible benefits (reduced lengths of stay) and risks (premature hospital discharges) of this guideline if it were to be used to identify patients for early discharge from the acute-care hospital to a more appropriate level of care. We hypothesized that acute hospital care could be provided at lower cost without compromising the quality of care.

Patients and Methods

The study was performed at Cedars-Sinai Medical Center, a large teaching community hospital that serves West Los Angeles, California. Most patients admitted to this hospital are cared for by physicians in private practice. The study was approved by the Institutional Review Board at the study hospital.

Patients

Patients consecutively admitted to the hospital were potentially eligible for inclusion in the study if they received a total knee replacement between January 1991 and April 1993. Patients were selected from the hospital database by *International Classification of Diseases* (9th revised), *Clinical Modification* (ICD-9-CM) codes.[13] Patients who underwent revision of a previous knee replacement or who had bilateral knee replacement were excluded from the study.

Practice Guideline

The guideline was developed through the consensus of two board-certified orthopedic surgeons and a board-

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TABLE 1.—*Risk Classification Criteria for Low-Risk Patients Having Total Knee Replacement**

Class	Criteria
I	Hypovolemia (at time of classification) Dehydration
IIa	Cardiopulmonary complications (at any time before classification) Acute myocardial infarction Pulmonary embolism Ventricular arrhythmias Supraventricular arrhythmias Pacemaker malfunction Respiratory acidosis True syncopal episode
IIb	Cardiopulmonary complications (at any time before classification) Hypotension Tachypnea Hypoxemia Acute-onset congestive heart failure or pulmonary edema
III	Surgical complications (at any time before the time of classification) Joint infection Iatrogenic fracture Wound dehiscence Wound infection Wound necrosis Seroma Dislocation of the implant Return to the operating room for orthopedic reasons
IV	Infectious complications (at time of classification) Fever Nosocomial infections being treated with intravenous antibiotics
Va	Other unstable conditions (at time of classification) Acute changes in mental state Severe anemia Hyponatremia Hypokalemia or hyperkalemia Severe hyperglycemia Drug toxicity Postoperative ileus Patient requires total parenteral nutrition Observed inability to take medications or fluids orally Substantial gastrointestinal hemorrhage New-onset stroke Serious medication reaction Other unstable comorbid conditions requiring continued acute care
Vb	Other unstable comorbid conditions (at any time before classification) Deep venous thrombosis Return to operating room for nonorthopedic reasons
VI	Functional status (at time of classification) Patients not yet able to transfer out of bed

*If a patient satisfies any of these criteria, the patient may not be at low risk and suitable for transfer or discharge from the acute-care hospital.

certified general internist (A.A., W.B., S.R.W.). We had previously studied a similar guideline for patients having total hip replacement.[14] Patients who did not have obvious reasons for continued hospital stay (as explicitly defined by the guideline) on the fourth through the seventh postoperative days were classified as being at "low risk" (Table 1). These patients were considered as possibly no longer requiring treatment in an acute-care hospital.

Complications—Explicit Review

We used a two-stage process to identify and classify patient complications. In the first stage, the data were abstracted from the medical record by a research nurse (L.C.). Complications of total knee replacement as defined for purposes of the study included death, the requirement of treatment in the intensive care unit, a systolic blood pressure of less than 100 mm of mercury, gastrointestinal distress and an inability to take food or medications orally, dehydration requiring intravenous therapy, acute mental state changes, hypoxemia while the patient was breathing room air ($Po_2 < 60$ torr or pulse oximetry < 90%), hypercapnia ($Pco_2 > 50$ torr), congestive heart failure, acute myocardial infarction, serious change in comorbid diseases, ventricular fibrillation, sustained ventricular tachycardia, asystole, unstable atrial fibrillation, unstable atrial flutter, supraventricular tachycardia, wound dehiscence, wound seroma, fever (temperature > 37.8°C [100.0°F]), postoperative pneumonia, anemia requiring transfusion, dislocation of the implant, peroneal nerve palsy, sciatic nerve palsy, seizure, postoperative hematoma, hemarthrosis, and deep venous thrombosis.

Patients who were determined to be at low risk on the fourth through the seventh postoperative days and who then suffered any of the explicitly defined complications after that day were considered to be possibly misclassified by the guideline. The medical records of these patients were then submitted for implicit review.

Complications—Implicit Review

In the second stage of the review, all complications occurring in low-risk patients after they became low risk were implicitly and independently reviewed by two physicians (a board-certified orthopedist and a board-certified general internist [A.A., S.R.W.]). These physicians rated whether transfer to a skilled nursing facility or discharge of the patient to home would have worsened the quality of care.[15] This method of judging quality of care has been used in previous investigations.[15]

Functional Status

Each patient's ability to transfer and walk was determined by examining the physical therapists' progress notes. If the physical therapy record was missing documentation, the last recorded value was used.

Resource Use—Lengths of Stay

The expected benefit afforded by the guideline was the projected reduction in the number of acute-care hospital bed-days. Lengths of stay were determined as per the midnight census. For each low-risk patient, the hypothetical number of acute-care hospital bed-days saved was defined as the number of actual acute-care hospital bed-days less the number of days in the acute-care hospital recommended by the practice guideline.

Patients who were deemed not suitable for transfer or discharge by the guideline were not included in the analysis.

Statistical Analysis

The primary end points of the study were the projected effect of the guideline on quality of care (misclassification rate) and the number of hospital bed-days that could have been saved. The misclassification rate was defined as the number of low-risk patients who suffered complications after they became low risk according to the guideline. Means are reported with standard deviations. The 95% confidence intervals (CIs) were calculated using the software package True Epi-Stat.[16] End points were tested using a type I error of .05.

Data Quality

The inter-rater agreement on the guideline classification of whether a patient had an obvious reason for a continued hospital stay on the fourth postoperative day was 95% (κ 0.89); fifth postoperative day, 95% (κ 0.85); sixth postoperative day, 95% (κ 0.64); and seventh postoperative day, 89% (κ 0.46). Inter-rater agreement on the implicit review of complications between the orthopedic surgeon and internist was 93% (κ 0.71).

Results

Demographics

A total of 206 patients were included in the study. Medical records were available for abstraction on 202 (98%) eligible patients. The mean patient age was 68.9 ± 10.9 years (mean ± standard deviation). Patient characteristics are described in Table 2.

The mean hospital length of stay was 8.0 ± 3.8 days, and the mean postoperative length of stay was 7.8 ± 3.6 days. Patients were able to transfer out of bed and begin physical therapy in an average of 1.6 ± 0.7 and 1.3 ± 0.6 days after their surgical procedure, respectively.

The discharge dispositions of the patients were as follows: 125 patients (61%) were transferred to a hospital-based skilled nursing facility, 64 (31%) were discharged to home, 3 (1%) were transferred to a free-standing skilled nursing facility, 1 (0.5%) died during the hospital stay, and 13 (6%) had a disposition other than these categories.

Guideline Classification

A total of 162 patients (78.6%) were at low risk during the fourth through the seventh postoperative days (Table 3). For example, for the patients who became low risk on the fourth hospital day, the postoperative length of stay was 7.3 ± 2.6 days (Table 3). None of these patients were discharged from the hospital before the fourth postoperative day. Had the guideline been applied to patients who became low risk at any time during the specified period, costs associated with 538 bed-days (223 bed-days per year) might have been reduced.

All patients were transferring out of bed, and many patients were walking substantial distances when they were classified as low risk according to the guideline (Table 4).

TABLE 2.—*Patient Characteristics (n = 206)*

Chorocteristic	Potients No.	Potients %
Sex, female	137	68
Surgery type		
Unilateral knee arthroplasty	196	97
Unicompartmental arthroplasty	6	3
Comorbid diseases		
Coronary artery disease	30	15
Chronic obstructive pulmonary disease	21	10
Diabetes mellitus	21	10
Rheumatoid arthritis	21	10
Congestive heart failure	18	9
Cerebrovascular accident	3	1

Explicit and Implicit Judgment of Quality of Care

A total of 29 patients (18%; 95% CI, 12%, 25%) suffered minor complications after they became low risk (Table 5). Implicit review determined that for 157 of these patients (97%; 95% CI, 93%, 99%), the quality of care would not have been compromised had they been transferred (or sometimes discharged home) to a more appropriate location when they became low risk. Patients whose care might have been compromised had they been transferred are listed in Table 6.

Discussion

Most patients recovering after total knee replacement had an uncomplicated clinical course and were possible candidates for early transfer or discharge from the acute-care hospital to a more appropriate level of care. Correspondingly, these patients suffered few clinically important complications after they were classified as low risk. Patients' actual length of stay exceeded the recommendation in all cases, which signifies an opportunity to safely shorten lengths of stay for these patients. There was also great variation among physicians in length of stay for low-risk patients, which indicates a lack of consensus about the most appropriate length of stay.[17] Clinical data such as those collected for this study may reduce this uncertainty. Reducing the length of stay for patients having a total knee replacement could sub-

TABLE 3.—*Patients With No Obvious Reason for Continued Acute Care in Hospital*

Postoperotive Doy	Potients ot "Low Risk" No.	Potients ot "Low Risk" (%)	Length of Stoy, doys*
4	112	(54)	7.3 ± 2.6
5	32	(16)	7.4 ± 1.4
6	13	(6)	11.0 ± 4.7
7	5	(2)	9.0 ± 1.2

*Postoperative days. The numbers represent the mean ± standard deviation.

TABLE 4.—*Distance Walked on the 4th Through 6th Postoperative Days by Low-Risk Patients Having a Knee Replacement (n = 157)*

Feet Walked	Postoperative Days 4th, No.	5th, No.	6th, No.
Unknown	12	5	2
0	6	2	1
1-10	14	1	0
11-25	13	7	4
26-50	19	7	2
51-150	40	8	3
>150	8	2	1

stantially reduce the cost of caring for these patients both at our hospital and on a national level.

Our study is limited in several ways. First, the data were collected retrospectively and only during the acute-care hospital stay (patient data were not collected after discharge from the acute-care hospital), and we cannot be certain that some patients would not have derived at least some benefit from continued stay in the acute-care hospital. A prospective study done with the data collected after hospital discharge would be necessary to exclude this possibility, however. Second, although we were able to conclude that low-risk patients may be discharged from an acute-care hospital earlier than is current practice, we are unable to determine whether these patients would be better suited going to a skilled nursing facility or to their home. Finally, this study was done at only one hospital.

The possible advantage of using an objectively derived guideline to prescribe the appropriate length of stay for patients with common conditions is the ability to predict the safety and efficacy of earlier hospital discharge. Our analysis allows discharge decisions to be based on clinical data rather than on economically derived data or on "customary and usual practice." These data also may be used to develop practice guidelines and clinical pathways and to determine the usual progress of patients after a knee replacement operation. Furthermore, early hospital discharge from an acute-care hospital, when appropriate, may benefit patients by reducing the risk of nosocomial infections and other iatrogenic complications.[18]

TABLE 5.—*Complications Occurring After the Patient Was Designated 'Low Risk' by Practice Guideline*—Results of Explicit Review*

Complication	Patients, No*
Fever (temperature >37.8°C [100°F])	20
Anemia requiring transfusion	9
Systolic blood pressure <100 mm of mercury	4
Hemarthrosis	4
Deep venous thrombosis	3
Congestive heart failure	2
Hematoma	1
Substantial change in comorbid disease	1
Total	29†

*Several patients had more than 1 complication.
†Complication rate, 17.9% (95% CI; 12.3%, 24.7%).

TABLE 6.—*Patients Who May Have Been Adversely Affected Had They Been Transferred or Discharged When They Became Low Risk**

Patient	Age, yr	Sex	Case Description, Treatment, and Outcome
1	67	F	Deep venous thrombosis developed on 8th postoperative day; anticoagulation therapy given; recovery uneventful
2	90	F	Received 2 units of packed erythrocytes on 5th postoperative day; mild congestive heart failure developed; oral furosemide given; recovery uneventful
3	73	M	Deep venous thrombosis developed on 6th postoperative day; anticoagulation therapy given; recovery uneventful
4	81	F	Fever and mild congestive heart failure developed after 6th postoperative day; 40 mg of furosemide IV and packed erythrocytes given; recovery uneventful
5	72	F	Fever and changes on ECG developed after 5th postoperative day; serial cardiac enzymes showed no evidence of acute myocardial infarction; 2 conflicting ventilation-perfusion scans showed no definite pulmonary embolism; treated with packed erythrocytes; recovery otherwise uneventful

ECG = electrocardiogram, IV = intravenous

*According to implicit review.

Acknowledgment

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* * *

Sleep's Siren Calls

Three hours of sleep is not enough to forget the world:
a 4 AM darkness pants damply against the window,
with deep, dull clangs and high frequency hisses the radiator launches
while beeper's unbloodied blade repeatedly pierces splayed-out senses.
I'd been dreaming too sweetly for this offensive—

the mind's first stirring is to question everything.

The inky apparitions piled in my clothes surrounded by name tag,
3×5 cards and clipboard menace my mind into chanting:
"Swarming vat of mental vapors let rise
barely contained visions of marked surprise
to put the steam again in sleepy eyes."

Nearly awake, I still question everything.

Like the wayward chutist wrapped in a web of branches
I wonder if I can make my arms and legs move.
As a creepy panic scrambles over exposed nerves
I count how many more call nights I have to endure
and wonder how other doctors shake this stupor—

do they also question everything?

Talks with patients, serious and humorous,
and conversations with 5 AM-punchy colleagues
drag back with me to my suite
"to get my one last hour of sleep"
crowded with dreams who visit, nurture and leave me

marveling that I questioned anything.

TIM VAN ERT, MD©
Selah, Washington

Articles

Ciguatera Fish Poisoning
A Southern California Epidemic

ERIK D. BARTON, MD; PAULA TANNER, REHS; STEVEN G. TURCHEN, MD; CYNTHIA L. TUNGET, PharmD; ANTHONY MANOGUERRA, PharmD; *and* RICHARD F. CLARK, MD, *San Diego, California*

Ciguatera fish poisoning results from the bioconcentration of a variety of toxins produced by marine dinoflagellates. Signs and symptoms vary widely, but it usually presents as gastrointestinal and neurologic complaints beginning shortly after the ingestion of fish containing the toxins. Symptoms may persist for months and sometimes even years. Although cases have been reported throughout the United States, epidemics are most common along tropical and subtropical coasts and usually involve the ingestion of large carnivorous fish. We review the literature and report the first epidemic of 25 cases of ciguatera fish poisoning presenting to area hospitals in Southern California that were successfully tracked by the Department of Health Services and isolated to fish caught off the coast of Baja California, Mexico.

(Barton ED, Tanner P, Turchen SG, Tunget CL, Manoguerra A, Clark RF: Ciguatera fish poisoning—A Southern California epidemic. West J Med 1995; 163:31-35)

In the Evening every one who had eat some of these fish (called Groopers) were seiz'd with Violent pains in the head and Limbs, so as to be unable to stand, together with a kind of scorching heat all over the Skin (. . . and numness in the joints . . .), there remained no doubt but that it was occasioned by the fish being of Poisoness nature and communicated its bad effects to every one who had the ill luck to eat of it even to the Dogs and Hogs. [O]ne of the latter died in about Sixteen hours after and a young dog soon after shared the same fate. (It was a Week or ten days before all the gentlemen recover'd).

JOURNALS OF CAPTAIN JAMES COOK ON HIS VOYAGES OF DISCOVERY, JULY 1774[1]

Ciguatera toxins are tasteless, odorless, heat-stable, and lipid-soluble compounds originating in dinoflagellate eukaryotic organisms that attach themselves to marine algae thriving in tropical and subtropical reef systems.[2-4] A variety of compounds, including ciguatoxin, maitotoxin, scaritoxin, palytoxin, and possibly okadaic acid, are thought to be involved. These toxins are passed up the food chain from small plant-eating fish to large predatory fish, with increasing concentrations at each succession. Toxins are found in virtually every part of the fish, but appear to be more concentrated in the head, organs, and roe.[5] Most fish appear to be unaffected by ciguatera toxins, although the mechanism of resistance is unclear. These toxins, however, have proved poisonous to a variety of animals (including mammals), birds, reptiles, crustaceans, insects, and humans.[6]

Ciguatera fish poisoning is considered a world health problem, with outbreaks documented in numerous coastal countries. It is prevalent in the tropical Caribbean and the subtropical North Atlantic and Pacific regions. Cases are being recognized with increasing frequency in the United States.[5,7] Certain weather patterns and ecologic disturbances such as earthquakes, typhoons, and tidal waves or tsunamis are thought to be some of the natural causes of outbreaks of ciguatoxin. These disturbances to reef systems cause the toxic organisms, normally residing beneath the sand, to swim and spread.[4-5,8] Human activities such as shipwrecks, underwater or shoreline explosions, military activities, or the construction of docks and piers have also been implicated.[9]

We report an epidemic of 25 cases of ciguatera poisoning on the Pacific Coast of the United States as discovered and tracked by the Department of Health Services in San Diego, California, over a four-month period.

Report of Cases

Patients 1 through 4

In March 1992, a 47-year-old woman sought care early in the morning at a San Diego-area emergency department with nausea, vomiting, loose stools, and neurologic complaints, including paresthesias of the face, arms, and legs. She also had dizziness and shortness of breath and noted that her symptoms began after consuming fish for dinner the previous night. She appeared dehydrated, had bradycardia at 40 beats per minute, and was admitted to the hospital for observation. The woman's 50-year-old husband also became symptomatic later that day and presented to the hospital with the family's two daughters for evaluation.

From the Department of Emergency Medicine, University of California, San Diego (UCSD), Medical Center (Drs Barton and Clark), the San Diego County Department of Public Health, Environmental Health Services (Ms Tanner), and the San Diego Regional Poison Center.

Reprint requests to Richard F. Clark, MD, UCSD Medical Center, 200 W Arbor Dr, #8676, San Diego, CA 92103-8676.

His symptoms included nausea, vomiting, and diarrhea, and he had tingling and numbness in his hands and feet. Their 14-year-old daughter experienced dizziness and a stomachache a few hours after eating, then vomited and had loose stools over the next 12 hours. She complained of tingling and numbness in her legs and fingers, feeling like they were "asleep." She also appeared dehydrated, with cool, moist skin and had difficulty walking. Her vital signs were normal. Her 16-year-old sibling reported similar symptoms, including the feeling that she could not move her legs and that her blankets were heavy on her legs. None of these patients had abnormal electrocardiograms or laboratory study results. Most of the gastrointestinal symptoms lasted less than 24 hours; all family members had persistent paresthesias and numbness in their extremities for several days after their fish meal, however.

The mother of the family reported that she had prepared a *lapo lapo* (a Filipino term for a grouper fish) for dinner on the night before the onset of symptoms. She had purchased the fish frozen from the garage of a private residence in the neighborhood. She prepared it by thawing, cleaning, and gutting it, then washed, breaded, and deep-fried the fish. She had also prepared and eaten a soup from the head of the fish. Environmental Health Services (EHS) staff from the Department of Public Health and from California Fish and Game investigated the garage where the fish was purchased and stopped any further sale of seafood from the facility. The owner admitted to selling the fish to the family and said that the fish was locally caught by a licensed commercial fisher; however, no information was given about the fishing boat or its owners. Frozen fish was impounded, along with the remains of the family's cooked fish, and sent to a laboratory in Hawaii to be tested for ciguatera toxin.

Patients 5 through 7

A few weeks after the first suspected group of poisonings, a local public health nurse informed the EHS of another family who had been seen in an area emergency department and diagnosed with ciguatera poisoning. Three of five family members had been treated with supportive measures including intravenous fluids for gastroenteritis, myalgias, chills, and paresthesias several hours after eating fish purchased from a local market. The two family members who were asymptomatic had not eaten the fish.

This time, EHS staff located the fisherman from the wholesale market where the fish had been bought. He reported that the implicated fish was a type of grouper called a cabrilla caught off the coast of Baja California, 468 miles southwest of San Diego and 235 miles off shore. He provided the name of the boat and information about its owners.

An interested researcher at Scripps Institute of Oceanography obtained a picture of the fish from the fisherman (Figure 1) and identified it as a flag cabrilla (*Epinephelus labriformias*, or red-tipped rock bass), a common channel water grouper that resembles the lapo

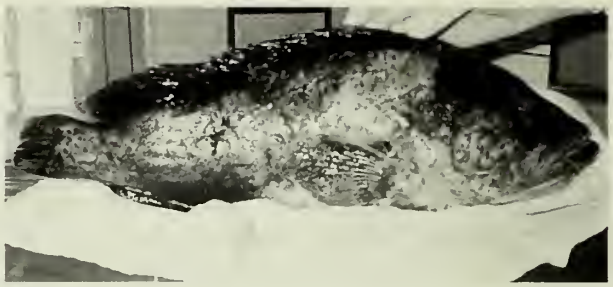

Figure 1.—The fish cabrilla (*Epinephelus labriformias*) is a channel water grouper found off the coast of Baja California, Mexico. This fish was one of the catch implicated in cases of ciguatera poisoning.

lapo grouper of the Philippines. This cabrilla is found off the coast of Baja, Mexico, south from Magdalena Bay and throughout the Gulf of California down to the coast of Peru. These particular fish were caught in the Alijos Rocks area off the Baja coast, 300 nautical miles west of Cabo San Lazaro, at a depth of 18 m (60 ft) (Figure 2).

Patients 8 through 24

In June 1992, three months after the initial outbreak of poisonings, a 66-year-old man came to another San Diego emergency department with vomiting, diarrhea, and neurologic symptoms about six hours after eating a fish that had been given to him by friends on a tuna seiner. His neurologic symptoms included sensitivity to cold, temperature reversal, paresthesias, difficulty walking, myalgias, and pruritus. He was treated supportively with histamine blockers, and his symptoms resolved over the next several days. The patient had made a stew of the entire 1.4-kg (3-lb) fish, including the head. He turned over a second smaller fish to EHS for testing.

The tuna seiner was identified within several days. All 16 crew members had been diagnosed with ciguatera poisoning by Memorial Maritime Medical Services. The physician involved said that the entire crew had temperature reversal, tingling of the palms and soles, and gastroenteritis and that one crew member had "cardiovascular

Figure 2.—The Alijos Rocks area, where the toxic fish was found, is located off the coast of Baja California, Mexico.

involvement," the nature of which was not specified. None of the crew needed to be admitted to a hospital, but blood specimens were taken from all involved and sent for testing. Crew members said that the cook on board the seiner had prepared a stew using the heads of fish caught on that trip. The location of this catch was at the coordinates of the Alijos Rocks area off the coast of Baja, corresponding exactly to the location of the previously involved catch. Frozen fish specimens were obtained and again identified as *E labriformias*, or flag cabrilla.

Patient 25

Several weeks later, a 42-year-old passenger from the same fishing expedition on the tuna seiner presented to a neurologist in San Diego with neurologic symptoms similar to those described for the crew, including night sweats and myalgias, that had persisted since the trip. He also stated that water felt cold on his hands and that he itched all over his body. He had also eaten the stew prepared on board from the fish heads. He had had 20 cabrilla in his freezer at home that he was preparing to ship to his relatives in New York, but had thrown them away after he became ill. His symptoms resolved over the next several months.

All fish and patient blood specimens were sent to the University of Hawaii, Manoa, where research is being done on ciguatera detection. Using a stick-enzyme immunoassay, a characteristic ciguatoxin-like compound was detected in the fish specimens. Ciguatera toxin levels in blood specimens from the affected persons were not able to be established when it was discovered that normal serum lipids interfered with the assay. Unfortunately, blood specimens were not retained for testing with more recently developed assays.

Discussion

Ciguatera has been an important cause of morbidity in the Caribbean and South Pacific, primarily in latitudes south of Hawaii. In the United States, cases have been reported from Florida, Louisiana, Massachusetts, New York, Vermont, District of Columbia, Texas, Kansas, Hawaii, Samoa, the Virgin Islands, and Puerto Rico.[5,7,10] Ciguatera is now endemic to Hawaii and Florida and found commonly in a variety of fish. More than 400 species of fish have been implicated in ciguatera outbreaks in one comprehensive report,[11(p63)] although more recent studies suggest that the actual number of infected species is low.[5] A total of 16 different fish were implicated in 172 cases of ciguatera in a recent series observed over a two-year period in Hawaii.[12] Ciguatera is not a new disease to US waters, being described as early as the 17th century. A number of cases have been recognized in nontropical areas of the inland United States, but most of these are attributed to fish imported from endemic areas.

Coral reef-dwelling and semipelagic fish are the actual vectors for the disease.[4] These large reef fish, including barracuda (*Sphyraena* species), grouper (*Epinephelus* and *Mycteroperca* species), red snapper (such as *Lutjanus* and *Sebastes* species), and amberjack (*Seriola* species), are caught near shorelines at depths of less than 91 m (300 ft). Ciguatera toxins are more concentrated in these species because they prey on smaller herbivorous fish that graze on macroalgae and detritus of coral reefs that contain the toxic dinoflagellates.[4,5] In addition, herbivore populations turn over quickly due to death or consumption and thus do not remain toxic for prolonged periods. Longer-living carnivorous species of fish at the higher end of the food chain may remain toxic for several years.

Outbreaks of ciguatera are thought to depend on a number of environmental factors. Water temperature, pH, and salinity may be important to the proliferation of toxic dinoflagellates.[13] *Gambierdiscus toxicus* is the predominant benthic dinoflagellate associated with ciguatera.[5] These organisms live on dead coral and thrive on a medium rich in algae, fungi, yeast, and bacteria. The presence of specific bacterias that synthesize the toxins after phagocytosis by the dinoflagellates is thought to be required for producing ciguatera toxin.[4]

Disturbances in coral reef environments by natural events such as storms, heavy rains, earthquakes, and tidal waves may precipitate outbreaks.[5,9] Toxic fish are often found on the windward side of tropical islands where wave energy and storm damage to reef systems is greatest. Human disturbances such as military activities in the Pacific islands, nuclear test explosions, construction, and shipping activities have also been shown to stimulate the proliferation of endemic ciguatera toxin.[9]

Epidemiologic physicians of the San Diego County Department of Public Health have suggested that the San Diego outbreak may have resulted from the unusual winter weather of 1991 and 1992, with several ocean storms and the El Niño phenomenon. The El Niño southern oscillation, which occurs approximately every ten years in an unpredictable pattern, causes widespread effects on the weather and water temperatures across the Pacific.[14-16] Profound changes have been observed in monsoon patterns, rainfall, agricultural production, and marine ecosystems during these oscillations. There is a rise in surface water temperature and even in mean sea level that results in a decline in marine productivity. The composition of phytoplankton species has been noted to change in the warmer waters of El Niño, with a predominance of zooplankton such as dinoflagellates.[14,15] An earlier study found a correlation between El Niño southern oscillation events and the proliferation of *Gonyaulax* species, the dinoflagellates responsible for paralytic shellfish poisons and cases of such poisonings in Washington State and British Columbia over a 40-year period.[16] Thus, such events might explain the sudden proliferation of *Gambierdiscus* dinoflagellates and the concomitant concentration of ciguatera toxins in flag cabrilla in coastal waters that were previously uninfected.

Although the cellular pathophysiology involving ciguatera remains unclear, several mechanisms of action have been suggested. The "opening" of sodium channels

in cell membranes through the occupation of calcium sites on these cells has been noted.[17] This could account for observed effects on action potentials in cardiac and neurologic tissue. Ciguatera toxin has also shown cholinergic as well as anticholinergic activity.[18] It is unclear, however, how other components such as maitotoxin and scaritoxin may contribute to the observed clinical effects.[19]

Diagnosis

The diagnosis of ciguatera is usually made by a history of fish ingestion followed by a typical combination of gastrointestinal, cardiovascular, and neurologic symptoms (Table 1). The onset of symptoms is similar to that of other food poisoning syndromes, often starting within 6 hours, with patients having nausea, vomiting, or diarrhea. Paresthesias of the extremities and numbness around the lips and tongue are common early symptoms and should alert a practitioner to ask about recent fish consumption. Almost all patients with notable exposures will seek care within 24 hours of ingestion.[4,5,7] Clinical presentations are highly variable and can be severe, including shock or coma. Eating the viscera, liver, or head of affected fish usually results in more serious poisonings because of the higher concentration of toxins in these tissues. One study reported mortality as high as 12%,[20] although actual mortality is probably lower.[21] Death is usually a result of cardiovascular or respiratory failure.

Cardiovascular effects associated with ciguatera are thought to result from a positive inotropic effect of the toxin on myocardium.[22] Dysrhythmias, including extrasystoles and bradycardia, and hypotension may occur in as many as a third of cases.[21] The treatment of shock may be required in some patients.

Neurologic complaints are almost pathognomonic to this disease and may persist for weeks to months, sometimes even years. Symptoms range from tingling or paresthesias to ataxia and lower extremity paresis.[4,5,7] Alterations in taste, myalgias and arthralgias, and fatigue are common symptoms. Temperature reversal is the most characteristic complaint and often manifests as cold objects feeling hot or burning to the touch. Other symptoms such as severe itching, photophobia, and psychiatric disturbances have been reported.[4]

A wide variation in the frequency and severity of symptoms has been noted.[12,23,24] These differences have been found to be associated with the type of fish eaten. The ingestion of herbivorous fish can result in exposure to more than one active ciguatera toxin.[23] Different species of carnivorous fish that feed on smaller herbivores may concentrate toxins differently. The dinoflagellate organism *G toxicus* elaborates both ciguatoxin and maitotoxin. Differences in biochemical alterations may promote other variants of toxins or active metabolites. Cardiovascular symptoms may occur more frequently in persons who eat carnivorous fish than in those who consume herbivores because of the increased toxin concentrations.[12] The patients in our series who ate the flag cabrilla primarily exhibited gastrointestinal and neurologic symptoms, although one woman did have bradycardia and hypotension.

TABLE 1.—*Symptoms of Ciguatera**

Symptom	*Cases, %*
Gastrointestinal	
Diarrhea	38-91
Vomiting	30-70
Nausea	33-44
Abdominal pain or cramping	35-43
Cardiovascular	
Bradycardia	9-37
Hypotension	10-25
Tachycardia	2-16
Musculoskeletal	
Arthralgias	33-86
Myalgias	30-85
Neurologic	
Extremity paresthesias	58-96
Circumoral or facial paresthesias	36-96
Temperature reversal	36-87
Asthenia	60-70
Headache	25-60
Pruritus	42-58
Paresis	10-33
Diaphoresis	18-29
Dizziness or vertigo	10-21
Ataxia	8-15
Dyspnea	8-12
Coma	8

*Adapted from Swift,[4] Kodama and Hokama,[12] Morris et al,[32] and Palafox et al.[37]

Ciguatera toxin has been associated with a variety of other disorders. One study reported the development of polymyositis in two persons after severe poisonings.[25] Ongoing research has shown ciguatera toxin-positive blood specimens in some persons previously diagnosed with the chronic fatigue syndrome, and in coastal cities, groups of patients with the chronic fatigue syndrome have a higher incidence of blood specimens positive for ciguatera toxins than patients with this syndrome who reside in midwestern cities (D.L. Parks, PhD, Nutrition and Food Science Dept, University of Arizona, oral communication, February 1994). Ciguatera toxin has been found in breast milk after acute exposure[26] and has been implicated in dyspareunia after possible sexual transmission.[27] Analysis of ciguatera toxins in blood specimens suggests that the toxin can be stored in adipose tissue for several years and that symptoms may recur during periods of stress such as exercise, weight loss, or excessive alcohol use (D.L. Parks, PhD, oral communication, February 1994).

The toxin is virtually impossible to detect in tissues or body fluid specimens without complex laboratory analysis. Mouse bioassays using extracts of fish tissues were reported in the early 1960s to determine the contamination of fish.[28] A direct radioimmunoassay was then developed using antibodies made in sheep and rabbits.[29] This

method allowed the testing of both fish specimens and human blood specimens for the presence of ciguatera toxins. Most recently, a rapid stick-enzyme immunoassay using horseradish and peroxidase-labeled sheep anti-ciguatera toxin antibody has been developed by Hawaii Chemtect International (Ciguatect) for detecting ciguatera toxins and toxins associated with diarrheic shellfish poisoning.[30] This test may soon be widely available to detect toxins in fish in only 15 minutes. Other products that will detect ciguatera toxins in human serum are also undergoing testing.

Treatment

The treatment of ciguatera poisoning has primarily been supportive. No known antitoxin is available. Previous treatments have been based on folk remedies and empiric drug therapy. Antiemetics, antidiarrheals, and intravenous rehydration are often necessary. Atropine sulfate has been used successfully for symptomatic bradycardia.[4,31,32] Intravenous calcium gluconate may have some theoretic benefit in counteracting the inhibition of calcium uptake by excitable membranes.[4,31] In addition, the use of magnesium-based cathartics should be avoided because of their possible calcium channel blocking action.[31] Pralidoxime chloride has been used as a cholinesterase reactivator based on laboratory data that ciguatera toxin acts as a cholinesterase inhibitor, although controlled studies have not been done.[32] Amitriptyline hydrochloride has been shown to provide variable relief for the neurologic symptoms associated with ciguatera poisoning, possibly related to a membrane-stabilizing effect through sodium channel blockade or through its anticholinergic activity.[33-35]

A study using intravenous mannitol reported an immediate resolution of most symptoms in 24 patients.[36] Mannitol, 0.5 to 1.0 grams per kg in a 20% solution given intravenously over a 10- to 30-minute period, is now considered the treatment of choice in both children and adults.[4,8,36-39] The mechanism of action of mannitol remains unclear, although it has been speculated to exert a membrane-stabilizing effect similar to that of amitriptyline.[36,37] No controlled studies have been done to confirm the efficacy of mannitol, and side effects such as dehydration can occur in some patients.[8,39] This risk is relatively low, however, and the immediate as well as the prolonged benefits of this treatment suggest that intravenous mannitol remains the preferred therapy at this time.

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Articles

Should Physicians Tell Patients the Truth?

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The medical literature suggests that most patients want to be told the truth about a diagnosis of cancer. Despite this evidence of their patients' wishes, physicians in many countries still hesitate to disclose this and other diagnoses. Physicians frequently ignore their patients' wishes when they consider the appropriateness of truth telling. A complete shift from nondisclosure to mandatory disclosure without considering patients' preferences may lead to serious harm to patients who do not want to be told the truth. Because physicians cannot satisfactorily treat patients without knowing their preferences toward disclosure of a diagnosis, I propose a simple strategy to break this long-standing ethical dilemma—physicians must develop the habit of inquiring about their patients' preferences.

(Asai A: Should physicians tell patients the truth? West J Med 1995; 163:36-39)

In Japan, the concept of informed consent has only recently been recognized.[1] Most Japanese physicians withhold important information about diagnosis and prognosis when their patients have cancer.[2-6] Articles in English-language journals suggest that many other countries face a similar dilemma.[7-13] Comparisons of patients' desires to be told a diagnosis of cancer and physicians' attitudes for disclosure show notable discrepancies. These comparisons suggest that patients are dissatisfied when physicians ignore their wishes.[3,8,10-15] Culturally specific attitudes of physicians and patients' families can be regarded as potential obstacles to meeting patients' wishes. Surveys also tell us that physicians should be aware that patients do not always want to be informed of a diagnosis of cancer. In some countries, many patients do not want to know the truth.[3,8,12,14,16]

Preferences for Disclosure of a Diagnosis of Cancer

How should physicians judge whether full disclosure is necessary? The criteria should not rest on physicians' preferences or their comfort, but should be in response to patients' satisfaction with current practice in their own countries. If most patients and their families are satisfied with the fact that patients are not informed of a diagnosis of cancer, then physicians need not change their attitudes. If patients are dissatisfied with current practice, it is problematic even though physicians may think that not telling the truth is good for their patients.

An international survey of 20 countries showed that oncologists estimated that a low percentage (<40%) of their colleagues used the word "cancer" or disclosed this diagnosis in Africa, France, Hungary, Italy, Japan, Panama, Portugal, and Spain.[11] In a survey in Japan, 67% of physicians would disclose the diagnosis to patients with early cancer, whereas only 16% would tell those with advanced cancer.[3] A 1991 survey of 1,171 Italian patients with breast cancer and their physicians showed that a minority of patients (47%) reported having been told that they had cancer.[13] In Spain, 42 of 167 cancer patients (25%) were correctly informed of their diagnosis.[10] A survey using several hypothetical situations evaluated variations in attitude among 260 European gastroenterologists to truth telling in cases of cancer. The results showed that gastroenterologists in northern Europe usually reveal the diagnosis to both the patient and the patient's spouse, but some would inform only the spouse with the patient's permission. They would conceal the truth if the cancer had metastasized. Gastroenterologists in southern and eastern Europe usually concealed the diagnosis from patients, in many cases even when the patient asked to be told the truth.[9]

In Greece, 500 healthy people were asked whether they would want to be informed of a diagnosis of cancer. A third of respondents replied yes, a third said no, and a third answered that it depended on the circumstances.[12] In 1986 an Italian public television survey showed that a sample population representative of the entire nation was more or less equally divided in its preference for truth telling in medicine.[8] In a survey of 1,023 patients who underwent upper gastrointestinal endoscopy in Japan, 58% of them wanted to be informed of the diagnosis if they had stomach cancer.[14] A survey of 183 outpatients in Japan revealed that 54% of them wanted to know a diagnosis of cancer.[15] A survey in a Spanish hospital reported that 71% of hospital health workers would want to know their own diagnosis should they suffer from cancer.[10]

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These data indicate that many patients want to be informed of a diagnosis of cancer. Although the numbers are limited, a discrepancy exists between patients' preferences and physicians' attitudes. Physicians may need to consider changing their attitudes based on patients' desire to know the truth.

Which Patients Should Be Told the Truth?

It is often argued that truth telling depends on the patient. The objective is to divide patients into two groups based on physicians' assessment of their patients' capacity to cope with the truth. One group includes patients to whom physicians can tell the truth without concern, and another includes those who physicians fear may be harmed by a full disclosure of information. The underlying assumptions are that the word "cancer" connotes death, that patients would be so desperate that they could not make autonomous decisions, and that they should be protected from this despair.[8,9]

In general, physicians decide to tell patients their diagnosis after carefully considering a patient's age, sex, personal history, occupation, family and social background, character, religion, and physical condition.[6,7] Physicians may be more comfortable discussing a diagnosis of cancer if the patient has a stable personality, strong family support, and religious beliefs. They may not inform patients of a diagnosis of cancer if the patient is female, older, less educated, or unemployed. Many Japanese physicians think that disclosure of a diagnosis of cancer should be determined in this way—case by case. As a result, no distinctive standard of disclosure has yet been established.[17] Because no standard criteria or widely accepted methods predict a patient's ability to cope with this serious situation, leaving the decision to physicians' impressions risks being biased by the physicians' own perceptions of cancer and death and own personalities. Even if this strategy is useful in identifying patients who can tolerate the diagnosis of cancer, it does not mean that physicians can distinguish between patients who want to be informed of their diagnosis and those who do not.

Physicians also regard the prognosis as an important factor in deciding whether to disclose a diagnosis of cancer. Many physicians would inform their patients about having early cancers, but are reluctant to disclose a diagnosis of incurable advanced cancer.[6,9] No evidence exists, however, that disclosure leads to despair. The data available consist of reports of patients in the United States where most patients have been satisfied with full disclosure.[18,19] A Japanese oncologist reported his impression that full disclosure to terminally ill cancer patients was not followed by depression or mental instability and seemed to result in improved terminal care.[20]

Another factor is the wishes of a patient's family. In Japan, Greece, Italy, and southern and eastern European countries, it is common to disclose a diagnosis of cancer first to a patient's family.[8,9,12] Some physicians would disclose a diagnosis to a cancer patient only when the family allows them to do so. Israeli oncologists are often faced with a spouse or children of a patient who insist that they must not disclose to the patient that he or she has cancer.[21] In a survey of patients' families in Spain, most patients' relatives preferred to avoid the word cancer and sometimes insisted that physicians not tell the truth to the patients.[10] An Irish physician also reported that it is appropriate to discuss the diagnosis first with the family.[9] A family would judge how and when they want to let a patient know in Ethiopia.[22] A belief held by many Chinese is that the sick are entitled to be treated as children and deserve protection.[23] In Japan, once a patient gets sick, the family usually treats the patient as incompetent. Physicians must ask whether they themselves and the patients' family are adequate substitute decision makers. Of 100 patients with breast cancer in Japan, 83 accepted disclosure of their own diseases, but only 21 advocated disclosure in the case of a family member.[24] A survey of 546 patients who knew they had cancer reported that two thirds desired a direct explanation, but only a third of their families wanted them to have it.[25] Several surveys on Japanese physicians showed that Japanese physicians are three to five times more likely to want to be informed of a diagnosis of cancer than they are to give this information to their patients.[3,26]

Both physicians and patients' families may assume that a patient will not tolerate a diagnosis of cancer—although they can.[26] The perceived discrepancy between what physicians and families want for themselves and for their patients may distort their assessment of patients' preferences. One survey done in Japan reported that physicians have practically no knowledge of their patients' preferences toward disclosure of a diagnosis of cancer.[27] A series of surveys done in the United States supported this conclusion.[28]

Who Should Decide?

Physicians need to recognize that some patients want to keep their right not to know information they may find intolerable. It would be paradoxically paternalistic for physicians to convey a diagnosis of cancer to patients who stated that they did not want to be informed. When offering truth, physicians must recognize that patients' choices should be respected not because they or others agree with those choices, but simply because it is the patients' right not to know.[16]

Being diagnosed with cancer is a uniquely personal disaster for many patients. First and foremost, it affects their own life; no one, including physicians or families, can take over their burden. Diagnostic information regarding one's body and life belongs to the person to whom it refers, not to family or physicians.[22] Therefore, a patient's wish to know or not to know the truth is the most important factor in determining disclosure.

Unlike many American patients, those from some cultures may be reluctant to express their wishes to their physicians. Physicians have to consider the factors that keep their patients from expressing their wishes in their own countries. Traditional paternalistic physician-

It is my custom to ask patients directly if they would like to be informed of a diagnosis of cancer should it develop. Some patients want to be informed; others do not. Physicians cannot predict whether patients would want this information. Even your family may not be able to predict what you want.

You are the only person who knows how much information you need. I want to respect your wishes to know or not to know the real diagnosis, even if it is against your family's wishes. **These questions have nothing to do with your current medical condition.** I will ask these questions periodically as long as our relationship continues. You can change your mind at any time. Please note that this is **not** a survey. These are your actual medical decisions and will be made part of your medical record.

I recommend that you keep a copy of your answers and discuss your decisions with your family immediately. If you have any problems with your family, please let me know.

- Would you want to know a diagnosis of an early and potentially curable cancer if it should develop?
  YES NO I do not know

If you chose I do not know or NO, to whom should we tell the diagnosis?

- Would you want to know a diagnosis of incurable cancer and its prognosis?
  YES NO I do not know

If you chose I do not know or NO, to whom should we tell the diagnosis?

- We will abide by your answers when we decide what and how much we should tell you. Is this acceptable to you?
  YES NO I do not know

If you chose I do not know or NO, what would you want us to do?

- Should we tell you a diagnosis of cancer even if your family insists that we not tell you?
  YES NO I do not know

If you chose I do not know or NO, what would you want us to do?

- Once you decide that a physician should tell a diagnosis of cancer to your family or whomever you choose, but not you, we will discuss your treatment with them and withhold all information from you. Is this acceptable to you?
  YES NO I do not know

If you chose I do not know or NO, what would you want us to do?

- We would like to know how much information you would want should cancer develop. Please choose one of the following:

  Diagnosis only
  Diagnosis and prognosis
  All of the above and choices of treatment (operation, chemotherapy, other) with their side effects and success rates of treatment
  All of the above and choices of life-sustaining treatment (if the disease should become terminal) with their side effects and success rates of treatment
  Other

Signature:

Figure 1.—A sample questionnaire is shown for patients undergoing routine cancer screening.

patient relationships,[6,8] physicians' power over patients,[29] requests by patients' families, and reluctance to question or discuss must be reconsidered.[30] For example, a Russian patient noted ". . . the doctor gives you medicine and you take it. No questions."[31(p334)] French patients rarely question the prescribed treatments.[32] Patients in Japan do not usually expect to be equal participants or involved in health care decision making.[33]

How can physicians know the minds of patients who are reluctant to ask or discuss medical issues, especially serious ones? Physicians must take the initiative to ask them if they want to know their diagnosis, even if it is unfavorable. If patients prefer to know their diagnosis, physicians also should ask them how much information they would like about the prognosis and whether they want to join the discussion of their own treatment. These questions must be asked in a systematic manner at the beginning of the patient-physician relationship—before any examinations and laboratory tests are done. For example, physicians can interview patients who undergo routine cancer screening or periodic health examinations. These questions can be asked along with the medical or personal history to avoid raising suspicion that the physician thinks that the patient has cancer. It is necessary to repeat these questions periodically because the answer given when patients are healthy may not predict patients' wishes when they are really ill. A sample questionnaire is included (Figure 1).

This inquiry might also be useful for American physicians who deal with patients from countries where physicians are paternalistic and withhold a diagnosis of cancer. By inquiring early in the relationship, physicians could decide whether to tell the truth based on patients' stated preferences. These patients may be reluctant to say what they really want to do; their expression of preferences might be subtle and indirect, and they might hesitate to refuse their physician's recommendation. It is also important to remember that physicians cannot predict patients' preferences solely from their cultural backgrounds. Many articles regarding attitudes of people from diverse cultures are available and provide characteristics of particular cultures, but it is doubtful that those data can serve as accurate guidelines to assess each patient in the clinical setting. Patients vary from one another even when their cultural origin is identical. These differences would require American physicians to pursue careful assessment of the desire for disclosure in patients from other countries.

Usefulness of This Strategy

It should be noted that meeting patients' preferences does not ensure their satisfaction with medical practice. It is possible that patients may regret asking to be informed of their diagnosis because of the grave nature of the information, the burden of lengthy discussions about prognosis, complications, and treatment, and consideration of life-sustaining treatment. Furthermore, we cannot know whether patients who have been unaware that they have had cancer are dissatisfied with the fact that they were not informed of their diagnosis. We also cannot anticipate the degree to which patients with cancer can be satisfied with the disclosure based only on their desires to know it when they are well.

Given this unpredictable situation, physicians should base their attitudes toward truth telling on their patients' wishes. The smaller the discrepancy between patients' desires to be told the truth and physicians' willingness to tell it, the more likely patients are to be satisfied with their physicians' practices. It is difficult to satisfy patients by ignoring their preferences.

A proposal to elicit patients' preferences toward the disclosure of a diagnosis of cancer should be validated in an appropriate manner. If my proposal is effective, patients will be satisfied with this strategy. Clinical research should be conducted to reveal its effectiveness. Methods that include randomization and case-control comparison are considered unethical, however. If investigators fail to give patients in the control group an opportunity to express their preferences about medical information, these patients may be deprived of an opportunity that would benefit them.

An alternative research method is a descriptive survey of all patients who are told a diagnosis of cancer based on their wishes. The outcome variable would be the patients' satisfaction brought on by the disclosure of a diagnosis of cancer. We need to ask patients directly if they are satisfied to have been told the truth or whether they regret their decision and would have preferred not to know. Lack of data regarding the satisfaction of uninformed cancer patients makes it impossible to quantitatively compare patients' satisfaction with or without the disclosure. Therefore, the utility of this strategy can be shown only by presenting data regarding the satisfaction of patients who are told a diagnosis of cancer based on their own preferences.

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Conferences and Reviews

Sinusitis

A Review for Generalists

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A frequent complication of the common cold, sinusitis is one of the most prevalent problems seen in general medical and emergency department practices. In addition, nosocomial sinus infection, particularly in intensive care units, is being recognized more frequently. Decision making about managing patients with sinusitis is based primarily on the history and, to a lesser extent, the findings of the physical examination.

(Reuler JB, Lucas LM, Kumar KL: Sinusitis—A review for generalists. West J Med 1995; 163:40-48)

Sinusitis is one of the most prevalent problems encountered in general medical practice. Acute bacterial sinusitis, the most frequent complication of the common cold, may be unrecognized or misdiagnosed. Some patients are predisposed to recurrent bouts of acute sinusitis, and chronic sinusitis may develop that presents as enigmatic facial or head pain. Finally, nosocomial sinusitis is being increasingly recognized in patients being treated in a hospital.

In most cases of sinusitis, clinical decision making rests on the history and physical findings. We review those aspects of sinusitis germane to general medical practice, including clinical and bacteriologic features, pathogenesis, special populations, treatment, and indications for radiographic imaging and surgical referral.*

Anatomy of the Sinuses

The accessory sinuses or air cells of the nose are called the paranasal sinuses. The frontal, ethmoid, sphenoid, and maxillary sinuses are lined with ciliated mucous membranes and are directly contiguous with the nasal cavity through the meatus of the superior, middle, and inferior nasal conchae arising from the lateral nasal walls (Figure 1). The maxillary sinus is inferior to the bony orbit and superior to the hard palate and has an ostium located superiorly and medially in the sinus, a location that impedes gravitational drainage.[1]

The ostium of the frontal sinus communicates with the nasal chamber at the frontal recess beneath the frontal sinus just ventral and superior to the infundibulum. The sphenoid sinus is just anterior to the pituitary fossa behind the posterior ethmoid sinuses, and its paired ostia drain into the sphenoethmoidal recess. Finally, the ethmoid sinuses comprise 3 to 15 air cells on each side, with each cell maintaining a separate drainage path to the nasal chamber. The lateral surface of this labyrinth forms the medial surface of the orbit.

The osteomeatal complex comprises the area between the middle and inferior turbinates at the confluence of the drainage of the frontal, ethmoid, and maxillary sinuses (see Figure 1). This area, where two mucosal layers come into contact, is predisposed to localized inflammatory change because of a disruption of mucociliary clearance, a resultant retention of secretions, and decreased sinus ventilation.

Pathogenesis

Four interrelated factors operate in the causation of sinusitis, including patency of the ostia, nasal airflow, mucociliary activity, and the nature and quantity of secretions. The sinus mucosa is similar to that in the respiratory tract and nasal passages. A mucous blanket is propelled toward the ostia by the underlying cilia, removing microorganisms, pollutants, and irritants. The obstruction of mucociliary drainage in the osteomeatal complex is thought to be a major cause of symptomatic sinus disease. Lower oxygen content in the sinuses facilitates the growth of organisms, impairs local defenses, and alters leukocyte function.[2] The swelling of the mucous membranes narrows the ostia and impairs the transport capacity of the mucociliary apparatus.

Viral upper respiratory tract infections and allergic rhinitis are the most common initiating factors in sinusitis.[3,4] Also, nasal polyps may cause sinusitis by impeding drainage and aeration of the antrum. Conversely, constant irritation from sinus infection may stimulate the growth of polyps by causing the nasal mucosa to duplicate in the form of a polyp. Barotrauma, as seen in airline pilots, may

*See also the editorial by J. W. Williams Jr, MD. "Sinusitis—Beginning a New Age of Enlightenment?" on pages 80-82 of this issue.

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
HCl = hydrochloride
OR = odds ratio
VA = [Department of] Veterans Affairs

result in barometric pressure stresses leading to altered sinus drainage, impaired ventilation, and the clearance of mucous secretions predisposing to acute sinusitis.[5] Swimming, diving, and abuse of topical nasal decongestants, as well as the presence of hypertrophied adenoids, deviated nasal septum, or nasal foreign body, may predispose to obstruction of the osteomeatal complex, as can the placement of nasotracheal or nasogastric tubes.[6] Finally, contiguous dental infection was the cause of maxillary sinusitis in 10% of cases reported from an otolaryngology referral practice.[7]

Bacteriology

The paranasal sinuses are normally sterile. In adults, acute sinusitis is most commonly due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.[4,8] In chronic sinusitis, anaerobic organisms, predominated by species of *Peptostreptococcus*, *Fusobacterium*, and *Prevotella* (formerly *Bacteroides*), are found in 88% of cultures, alone or in conjunction with aerobes, most commonly *Streptococcus* species or *Staphylococcus aureus*.[9-11] In those with underlying immune deficiencies, such as patients positive for the human immunodeficiency virus, organisms identified may include gram-negative species and opportunistic fungi.[12,13]

In patients with acute and chronic sinusitis, the presence or type of bacteria cannot be adequately determined by the use of nasal swabs.[3] Therefore, when accurate characterization of bacteria is warranted, either direct sinus aspiration or culture material obtained at the time of an operation is necessary.

Clinical Features

Acute Sinusitis

The symptoms of acute sinusitis, including facial pain, headache, purulent nasal discharge, decreased sense of smell, and fever, are nonspecific and often difficult to differentiate from those of the common cold and allergic rhinitis.[14,15] Most studies comparing the history and physical examination with the standard procedure, antral puncture, for diagnosing maxillary sinusitis have been conducted in otolaryngology practices.[7,16,17] In these groups, subjective or objective purulent nasal discharge was most helpful in differentiating sinusitis from rhinitis. Antral puncture, however, is not a practical diagnostic procedure for primary care providers.

A recent study of primary care patients compared general practitioners' clinical diagnosis of maxillary sinusitis with the use of ultrasonography of the sinuses (a technique used primarily in Europe).[14] Using an algorithm of five weighted symptoms—preceding common cold, purulent rhinorrhea, pain on bending, unilateral maxillary pain, and pain in the teeth—the proportion of correct diagnoses increased from 40% to 55%. Diagnosis with the algorithm was more accurate than clinical diagnosis by general practitioners, but inaccuracy and uncertainty persisted.

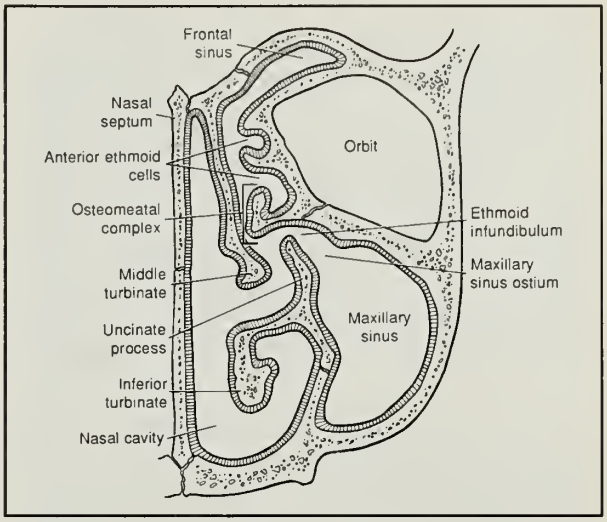

Figure 1.—The diagram shows the paranasal sinuses.

Finally, a recent study done in a general medicine clinic of a VA medical center evaluated 247 men (median age, 50 years) presenting with rhinorrhea, facial pain, or self-suspected sinusitis.[18] The prevalence of sinusitis in this group, as defined by radiographic changes, was 38%. Logistic regression analysis showed five independent predictors of sinusitis, none of which were both sensitive and specific alone: maxillary toothache (odds ratio [OR], 2.9), transillumination (OR, 2.7), poor response to nasal decongestant or antihistamine therapy (OR, 2.4), colored nasal discharge noted by the patient (OR, 2.2), or mucopurulence seen during examination (OR, 2.9); used in combination, the predictive probability varied from 92% (all 5 features present) to 9% (none present). An important finding is that the overall clinical impression was more accurate than any single historical or examination finding, suggesting that the gestalt is useful to diagnose sinusitis when the probability of disease is judged to be high, and antecedent upper respiratory tract infection or facial pain were not predictive of sinusitis. Whether these findings are applicable to other groups (such as younger patients) or settings (clinicians without a special interest in sinus disease or access to or training with special transillumination instruments) is not known.

Sinusitis and Immunosuppression

The clinical presentation of sinusitis in immunocompromised patients, particularly those with severe leukopenia, may be subtle, making an early diagnosis difficult and increasing the likelihood of a fulminant and even fatal course.[19] The common underlying diseases include aplastic anemia, leukemia, bone marrow transplantation, and primary immunodeficiency diseases. Besides the

common sinus pathogens, atypical mycobacteria, *Aspergillus* species, Phycomycetes, *Fusarium* species, and cytomegalovirus have been reported to cause sinusitis in these patients.[19]

Sinusitis occurs in patients with severe leukopenia and may present as fever of unknown cause, rhinorrhea, or facial edema. A lesser degree of pain, edema, erythema, and pus formation is due to an impaired inflammatory response. The physical examination may show pale or gray areas in the nasal mucosa that are the earliest signs of tissue infarction due to a fungal invasion of blood vessels. Rather than purulent, the discharge is often turbid.

Of particular concern is the invasive form of fungal sinusitis that may extend across the mucosa into bone and adjacent structures, including the orbits, brain, and cavernous sinus.[20] The diagnosis of invasive infection can be made only after the histologic demonstration of hyphae. Early diagnosis and extensive surgical debridement are crucial for survival.

Rhinocerebral mucormycosis is a fulminant infection similar to invasive aspergillosis that occurs in patients with diabetic ketoacidosis or acute leukemia. The infection originates in the nasal cavity and spreads through the sinuses to the orbit and central nervous system, causing thrombosis and tissue necrosis. Patients exhibit a black nasal mucous membrane, cranial nerve palsies, proptosis, and an altered mental state. Treatment involves emergency aggressive surgical debridement and the administration of parenteral amphotericin B.[21]

Hospital-Acquired Sinusitis

Hospital-acquired acute sinusitis is due to a different microbial flora than community-acquired acute sinusitis. *Staphylococcal aureus*, *Pseudomonas* species, *Klebsiella* species, and other gram-negative organisms are found in sinus puncture studies.[22-24] About 35% to 40% of cases of hospital-acquired sinusitis are polymicrobial infections and are often bilateral. The incidence of sinusitis in hospitalized patients requiring long-term ventilation varies widely depending on the definition of sinusitis (radiologic versus culture) and the patient population. Two recent studies using a combination of clinical signs, radiologic diagnosis, and aspirate confirmation found that, after two to four days of ventilation, those patients with nasotracheal intubation had a 0% to 40% greater incidence of nosocomial sinusitis compared with patients with orotracheal intubation.[6,24] Other predisposing factors for sinusitis in inpatients include nasogastric tubes, nasal packing, cranial and facial fractures, and the use of corticosteroids and of antibiotics.[22,25] Unexplained fever or leukocytosis and purulent nasal discharge may be the major clinical features that lead to the recognition of acute sinusitis in an intubated patient.

Allergic Sinusitis

Allergic sinusitis occurs in conjunction with allergic rhinitis. The mucosal changes in the sinuses are the same as seen in patients with allergic rhinitis. Symptoms usually consist of stuffiness, itching and burning of the nose, frequent bouts of sneezing, recurrent frontal headache, and a thin nasal discharge. Headache that is located between the eyes or in the frontal area is a common symptom and results from edema and swelling of the soft tissues. Allergic rhinitis may lead to polyp formation, and similar polypoid changes in the mucosa of the sinuses are seen commonly in patients with allergic sinusitis.

Although the term allergic sinusitis is commonly used, sinus disease associated with severe allergic rhinitis has never been documented radiographically. Single photon-emission computed tomography has been used to assess the metabolic activity and dynamic physiology of the sinuses.[26] Three patients with ragweed allergic rhinitis had a strongly positive skin reaction, were markedly symptomatic, their nasal mucosa was edematous, and their sinus x-ray films were normal. Single photon-emission computed tomographic imaging demonstrated substantial hyperemia of the sinuses and increased uptake in bones around the sinuses, which resolved after the ragweed season ended. This study shows that the dynamic process in the paranasal sinuses is similar to that seen in the nasal mucosa of allergic patients.

Chronic Sinusitis

Acute suppurative sinusitis is any bacterial infection in a paranasal sinus that lasts from one day to three weeks. When the infection lasts from three weeks to about three months, it is diagnosed as subacute sinusitis. A symptom complex of purulent nasal discharge, nasal obstruction, facial pain, headaches, chronic cough, and halitosis persisting longer than three months is labeled chronic sinusitis.[27] During the acute and subacute stages, the epithelial damage in the sinus is usually reversible, whereas in chronic sinusitis the mucosal damage is frequently irreversible, often requiring surgical therapy for better drainage and ventilation of the sinus. Patients with chronic sinusitis may have bouts of acute sinusitis superimposed on chronic disease.

Pain is typically absent in patients with chronic sinusitis, except in those with an infected frontal sinus. In this latter group, most patients complain of headache that is a dull, constant ache. In patients with chronic sinusitis, the only symptoms may be nasal obstruction, postnasal drip, chronic cough, hyposmia, and unpleasant breath.

The relationship of sinusitis and asthma is unclear. Clinically confirmed sinusitis occurs in about 17% to 30% of patients with known asthma.[28,29] Approximately 12% of patients with chronic sinusitis have asthma, and this may be restricted to those with extensive sinusitis by computed tomography (CT).[30,31] An equal number of radiologic sinus abnormalities have been found in patients with asthma, regardless of whether their asthma was mild or severe.[29]

Several mechanisms are postulated for the relationship of sinusitis to asthma. It is possible that the pulmonary aspiration of infected sinus secretions could lead to a secondary bronchitis, resulting in asthma in susceptible patients. In a small study of patients with sinusitis

TABLE 1.—*Complications of Sinusitis*

Intracranial	*Extracranial*
Meningitis	Osteomyelitis
Epidural or subdural empyema	Orbital cellulitis
Brain abscess	Subperiosteal abscess
Cavernous sinus thrombosis	Orbital abscess
	Blindness
	Superior orbital fissure syndrome
	Epiphora

alone or sinusitis with asthma, there was no demonstration of the pulmonary aspiration of radionuclide-labeled maxillary sinus secretions.[32]

Sinusitis could also result in parasympathetic stimulation and reflex bronchospasm. Several, but not all, studies of animals and humans have shown that electrical, mechanical, or irritant-induced stimulation of the nasopharyngeal or sinus mucous membranes resulted in bronchoconstriction, as evidenced by increased airway resistance or a fall in pulmonary function.[33,34]

With the resolution of sinusitis, the clinical course of asthma may improve.[35] In one study, 50 adults with medically refractory sinusitis and asthma underwent a surgical procedure with an improvement or cure of their sinusitis.[36] All had symptomatic improvement in asthma, and most of the 28 patients on long-term corticosteroid therapy had a sustained reduction or discontinuation of the medication.

Complications of Sinusitis

The complications of sinusitis are listed in Table 1. Intracranial complications are more commonly seen with infection of the frontal and ethmoid sinus because of their proximity to the dura and drainage of the diploic veins from the frontal sinus into the dural veins. Sinusitis is the primary source of infection in as much as two thirds of patients with intracranial abscesses[37] and 5% of cases of community-acquired bacterial meningitis.[38]

Extracranial complications most often involve the orbit and occur more commonly in patients with ethmoid sinusitis because of the thinness of the orbital wall and its close proximity to the sinus and valveless ophthalmic venous system. These veins communicate between facial, sinus, orbital, and intracranial veins and drain directly into the cavernous sinus. Although orbital complications are seen more often in young children, adults and older children tend to have more severe involvement.[39]

Orbital complications can range from edema of the eyelids, orbital cellulitis, subperiosteal abscess with exophthalmos, and chemosis, to orbital abscess with pronounced exophthalmos, chemosis, and visual impairment, and finally, progression to cavernous sinus thrombosis. Blindness can result from these orbital complications.[40] Cavernous sinus thrombosis should be suspected in patients with bilateral ophthalmoplegia and loss of vision. The diagnosis of orbital complications is based on clinical and CT or magnetic resonance findings.

Epiphora may result from chronic inflammation of the nasal mucosa. It occurs due to either stenosis of the nasolacrimal duct or obstruction of its orifice in the inferior meatus. In patients with ethmoid sinusitis, inflammation may extend to the lacrimal sac and result in tearing.

The superior orbital fissure syndrome may occur in patients with acute or chronic sphenoid sinusitis. Clinically, there is palsy of the nervus abducens (VI) followed by involvement of the third, fourth, and fifth cranial nerves, orbital pain, exophthalmos, and ophthalmoplegia. Finally, recurrent attacks of sinusitis may result in osteomyelitis of the orbital plate or frontal or sphenoid bones.

Differential Diagnosis

Other causes of facial pain and headache that may mimic acute sinusitis include migraine and cluster headache, trigeminal neuralgia, pain originating from teeth, temporomandibular disorders, and temporal arteritis. It may be difficult to differentiate patients with acute sinusitis clinically from patients with protracted respiratory symptoms, both cough and nasal discharge, because these can also cause headache. Headache due to sinusitis, however, is aggravated by bending forward, coughing, or sneezing.

Diagnostic Studies

In primary care practice, acute sinusitis is generally a clinical diagnosis based on the history and physical examination findings. The paranasal sinuses may be visualized by standard radiography, including occipitomental (Waters'), occipitofrontal (Caldwell's), and lateral and oblique (Rhese) views.[41] A recent study suggested that a

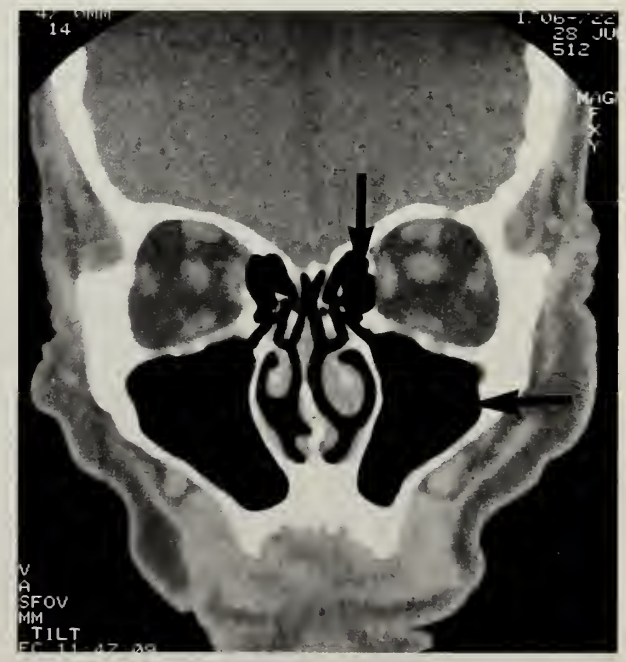

Figure 2.—A computed tomographic scan shows a normal maxillary sinus (**lower arrow**) and ethmoid sinus (**upper arrow**).

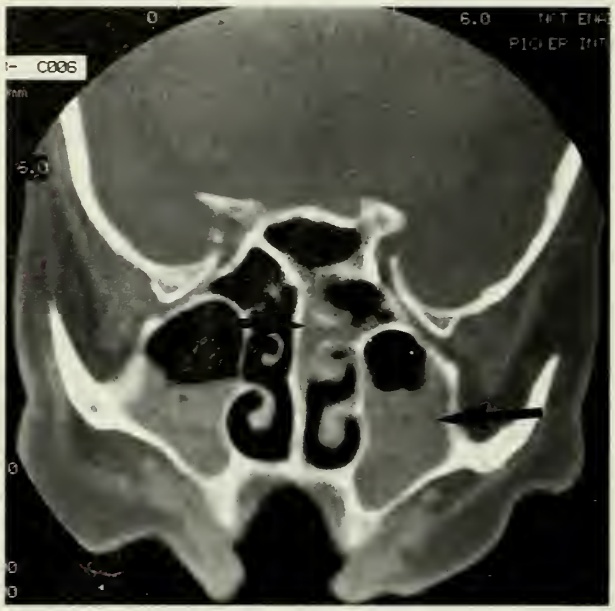

Figure 3.—A computed tomographic scan shows mucosal thickening and an air-fluid level in the left maxillary sinus (**lower arrow**) and mucosal thickening in the left ethmoid sinus (**upper arrow**) and left middle turbinate compared with normal turbinates on the opposite side.

single Waters' view was adequate for evaluating acute maxillary sinusitis in general medical patients with a high prevalence of sinusitis,[42] but it was not good for evaluating frontal, ethmoid, or sphenoid sinusitis. Because acute sinusitis is such a common and self-limited disorder, however, there is no consensus on how standard radiography should be used by primary care providers in the initial clinical evaluation of sinusitis.

Computed tomographic scanning shows excellent resolution of the paranasal sinuses, clarifying the anatomic relationships and variations that may play a role in sinusitis (Figures 2 and 3).[43] Recent studies evaluating the operating characteristics of CT scanning for sinusitis have shown that about 16% of persons without sinus-related symptoms will have abnormalities of the paranasal sinuses on CT scanning whereas only 62% of patients with sinus-related symptoms actually have CT scan evidence of sinus abnormalities.[44] The primary roles of CT scanning are to diagnose sinus disease when the differential diagnosis is not clear and to define the anatomy before an anticipated operation. Computed tomography is not used in the routine evaluation of acute sinusitis. Although the role of magnetic resonance imaging has yet to be defined in sinus disease, published articles suggest that it offers little in addition to CT, unless there is concern for a malignant neoplasm, fungal concretions of the sinuses, or intracranial complications.

More recently, diagnostic nasal endoscopy has been advocated as a primary evaluation strategy in those patients with recurrent or chronic symptoms.[45] This procedure, which can be done simply in the office by an otolaryngologist, provides a clear view of the anterior nasal cavity, including the middle meatus. Many now advocate that nasal endoscopy should supplement the diagnostic evaluation in all patients with chronic and recurrent acute sinusitis and that CT should be used either when endoscopy fails to explain the symptoms attributed to sinusitis or to define the anatomy before surgical therapy. In this regard, nasal endoscopy may serve as a screening test for deciding which patients require CT.

Medical Management

There are no proven methods to prevent acute sinusitis, although some authors recommend a prompt use of decongestants at the start of a viral upper respiratory tract infection in patients with a history of sinusitis. The treatment of conditions that may predispose to sinusitis, such as allergic rhinitis, nasal structural abnormalities, or dental root infection, may lessen the risk. Finally, adequate antimicrobial therapy for acute sinusitis, both in drug selection and duration, may help reduce the incidence of permanent mucosal damage and subsequent chronic sinusitis (Table 2).[7]

Timely adequate antibiotic coverage is the mainstay of the treatment of acute sinusitis, the goal being to relieve symptoms, prevent the development of acute complications, and avoid the development of chronic sinusitis.[46] Because there is no correlation between the organisms identified on nasopharyngeal culture and the causative agent found on sinus aspiration, antibiotic therapy is empirically directed at the most likely causative organism. Studies of sinus punctures before and after treatment have shown certain antimicrobial agents to be effective in cases of acute, community-acquired sinusitis, including combinations of trimethoprim and sulfonamides, aminopenicillins, and some cephalosporins, such as cefuroxime axetil.[3,14,46–49] No consensus exists about the duration of therapy. Although 10-day courses were adequate in these studies and many authors advocate 14-day regimens for the treatment of acute sinusitis,[50,51] a recent controlled trial showed equal efficacy between 3-day and 10-day regimens using trimethoprim and sulfamethoxazole.[52] In general, longer (10 to 14 days) duration therapy is standard practice.

An estimated 25% of *H influenzae* and *Moraxella catarrhalis* is β-lactamase–producing in cases of maxillary sinusitis in adults in some communities and, therefore, resistant to aminopenicillin drugs.[51,53] The combination of trimethoprim-sulfamethoxazole provides coverage (is bactericidal) against these β-lactamase–producing organisms, and generic products may even be less expensive than the aminopenicillins.[53,54] Agents such as cefuroxime axetil are effective against these resistant organisms, as well as *S aureus*. The combination of amoxicillin and clavulanate potassium provides a similar broad-spectrum bactericidal coverage in acute sinusitis and has been effective clinically and in sinus puncture studies.[55–57] All of these agents are first-line choices for the treatment of acute sinusitis, with trimethoprim-sulfamethoxazole being the agent with the broadest coverage for the least expense (see Table 2) and

TABLE 2.—*Management of Sinusitis*

Type of Sinusitis	*Therapy*		*Usual Adult Dosoge, mg orally/doy*	*Price, $**
Acute sinusitis				
Community-acquired.....	Antibiotic			
	Primary:	Trimethoprim-sulfamethoxazole, DS†	160-800, 2×	2.28
		Amoxicillin‡	500, 4×	10.92
	Alternate§:	Amoxicillin-clavulanate potassium	500-125, 3×	59.00
		Cefuroxime axetil	250, 2×	52.00
		Cefixime	500, 1×	50.00
		Clarithromycin	500, 2×	55.00
	Adjunct			
	Intranasal‖ or oral decongestant			
	Seek urgent otolaryngology referral for complications of sinusitis			
	Seek elective otolaryngology referral for >3 episodes/yr			
Hospital-acquired	Antibiotic			
	Primary:	Imipenem		
		3rd-generation parenteral cephalosporin		
		Either β-lactamase–resistant penicillin, ticarcillin disodium-clavulanate potassium, or piperacillin sodium-tazobactam sodium with an antipseudomonal aminoglycoside		
	Alternate:	Substitute aztreonam for the antipseudomonal aminoglycoside coverage listed above		
		Fluoroquinolone and ampicillin		
	Adjunct			
	Remove foreign body if associated (nasogastric or nasotracheal tube, packing)			
	Seek urgent otolaryngology referral			
Special groups				
Immunocompromised—HIV-positive, neutropenic, diabetic ketoacidosis	Antibiotic			
	Primary:	Coverage for gram-negative bacteria and opportunistic fungi		
	Adjunct			
	Seek urgent otolaryngology referral			
Allergic sinusitis.....	Antibiotic			
	Primary:	Treat acute exacerbations the same as community-acquired acute sinusitis		
	Adjunct			
	Decongestant‖			
	?Topical corticosteroid			
	?Antihistamine			
Chronic sinusitis	Antibiotic			
	Primary:	Treat acute exacerbations the same as community-acquired acute sinusitis		
	Adjunct			
	Decongestant‖			
	?Topical corticosteroid			

DS = double strength, HIV = human immunodeficiency virus

*Average wholesale price for a 10-day supply.

†Not effective in sinusitis following dental procedures where anaerobes may be present.

‡Aminopenicillins should be used for first-line therapy only where community prevalence of β-lactamase–resistant *Haemophilus influenzae* is low.

§Alternates are equally efficacious, but more expensive; if treatment response is incomplete after a 10- to 14-day regimen with a primary antibiotic, a 14- to 21-day course of an alternate antibiotic is recommended.

‖To prevent a rebound phenomenon, intranasal decongestants should not be used for more than 7 days.

aminopenicillins being used in sulfa-allergic patients in areas with a low prevalence of antibiotic resistance. Cefuroxime axetil, cefixime, and amoxicillin-clavulanate are considerably more expensive alternatives. New macrolide antibiotics, such as clarithromycin, may also be efficacious as first-line agents.[58,59]

We advocate using trimethoprim-sulfamethoxazole for initial treatment, unless the patient is allergic to sulfa or the sinusitis occurs after a dental procedure; amoxicillin or ampicillin should be used only if β-lactamase–producing organisms are uncommon, as determined by sensitivity testing in the locale (Table 2). If there is only partial clinical resolution after 10 to 14 days of taking a first-line antibiotic, a second course of treatment using a β-lactamase–resistant drug such as amoxicillin-clavulanate or a second- or third-generation cephalosporin should be initiated. Although some authors advocate confirming the diagnosis with plain radiography (or CT) after treatment fails with a first-line agent,[46] further study is needed to clarify whether imaging at this point alters outcomes.[60]

The antral sinus should be aspirated to detect causative organisms in patients with hospital-acquired sinusitis and in immunocompromised patients because of the increased prevalence of fungal, gram-negative, and polymicrobial infections. In patients with nosocomial infection and while awaiting culture results, or if treating empirically, the use of a β-lactamase–resistant antipseudomonal penicillin such as piperacillin, mezlocillin, or ticarcillin disodium and clavulanate potassium or piperacillin sodium and tazobactam sodium, in combination with an antipseudomonal aminoglycoside, is recommended. Other first-line options include a third-generation cephalosporin with enhanced antipseudomonal activity, such as ceftazidime or cefoperazone sodium, with or without an additional antipseudomonal aminoglycoside, or imipenem. Alternative drug regimens include a fluoroquinolone antimicrobial agent and ampicillin or substituting aztreonam for the aminoglycoside in the previous regimens.[53] Nondrug therapy includes the removal of any obstructing foreign body (such as a nasogastric or nasotracheal tube) and referral to an otolaryngologist for therapeutic antral lavage or surgical drainage.

In addition to using antimicrobial agents, the treatment of acute sinusitis includes facilitating adequate drainage by reducing tissue edema and maintaining ostial patency. Adjuncts to antimicrobial therapy that have been reported anecdotally include pharmacologic measures such as oral and topical decongestants, antihistamines, topical corticosteroids, expectorants, and analgesics. Nonpharmacologic measures include saline sprays and steam inhalations. A paucity of scientific data is available to support most of these adjuncts, however, and their use has been based on theoretical considerations and favorable clinical impressions. The average patient with acute sinusitis will have rapid subjective improvement within the first five days of treatment that precedes radiographic improvement.[61]

Oral vasoconstrictors, known as decongestants, that are available over-the-counter or as a prescription, are pseudoephedrine, phenylpropanolamine, and phenylephrine. These agents are sympathomimetic, α-adrenergic agonists that reduce nasal blood flow. Because they are parenteral oral decongestants, they have the theoretical advantage over topical agents to act on tissues deep within the osteomeatal complex to decrease tissue congestion and facilitate drainage. In patients with chronic sinusitis, a single 100-mg dose of phenylpropanolamine decreased nasal airway resistance and increased the functional osteomeatal size.[62] Although concerns have been raised about potentiating hypertension in patients taking oral decongestants, a number of studies have failed to demonstrate clinically important changes in heart rate or blood pressure in normotensive or hypertensive subjects.[63-65]

Topical (intranasal) decongestants have also been shown to increase nasal airway patency in patients with rhinitis, which act locally to decrease nasal edema and facilitate sinus drainage through the ostia.[66] Nasal sprays such as 0.5% phenylephrine hydrochloride (HCl) and 0.05% oxymetazoline HCl may provide immediate symptomatic relief. Other common intranasal decongestants are naphazoline HCl, tetrahydrozoline HCl, and xylometazoline HCl. Intranasal decongestants should be administered with the head erect, one to three sprays in each nostril, two to three times a day for three to seven days. Prolonged use may cause rebound vasodilatation, called rhinitis medicamentosa, which may result from the inhibition of α-adrenergic receptors due to high local concentrations of the drug, chronic chemical irritation, and reactive hyperemia.[51,67,68]

No studies have been done to show whether or not antihistamines are beneficial in patients with acute or chronic sinusitis. Antihistamines have both anticholinergic and decongestant properties to inhibit secretion and, therefore, are relatively contraindicated in patients with acute sinusitis; otolaryngologists do not recommend using antihistamines in this situation due to concerns of the drying of mucous membranes and interference with the clearing of secretions.[50]

Topical corticosteroids have been reported to reduce local sinus ostial inflammation and so increase functional ostial diameter, but there are no adequate data to justify their use in all patients with sinusitis. Many advocate the use of topical corticosteroids for patients with allergic rhinitis or sinusitis or in patients with chronic sinusitis.[50,69] In a recent placebo-controlled, double-blind study of the use of intranasal steroids in an adult population recruited from allergy clinics, their use with a broad-spectrum antibiotic in acute sinusitis had limited efficacy; there was only a trend toward lessening symptoms and decreasing inflammation.[70]

Expectorants such as guaifenesin are used by some in an attempt to thin secretions and aid in drainage, although there are no data related to their use in sinusitis. Analgesics are used purely as symptom control in those patients with substantial facial pain or headache. The use of nonpharmacologic measures is not supported by data, but many of these methods seem to provide symptomatic relief.[50,69] They include steam inhalation to liquefy secretions and moisturize dry, inflamed mucous membranes. Topical saline spray or irrigation with a saline solution two or three times a day may provide a mild decongestant

TABLE 3.—*Indications for Referral to an Otolaryngologist**

Acute Sinusitis
Complications
Deterioration within 2 days
Treatment failure after 2 courses of appropriate antibiotics
Frequent recurrences (>3 episodes/year)
Nosocomial infections
Immunocompromised hosts
Chronic Sinusitis
Treatment failure (or medically refractory)
Persistent nasal polyps with nasal obstruction

*See text for discussion.

effect, liquefy secretions, and moisturize the mucous membranes while providing some short-term symptomatic relief.

Chronic sinusitis is a disease of mucosal damage and is not primarily an infectious state.[71-73] Acute infectious exacerbations of chronic sinusitis should be treated similarly to acute sinusitis, but for treatment durations of three or more weeks.[27,51] Some authors advocate treatment in these situations with antibiotics such as penicillin, ampicillin, clindamycin, or amoxicillin-clavulanate to eradicate anaerobes as well as the major organism seen with acute exacerbation.[53] In addition to treatment with antibiotics for acute exacerbations, the use of decongestants and topical corticosteroids may aid in reducing the inflammatory response in patients with both acute flare and chronic infection.[74-76] A multimodal approach has been advocated, including administering antibiotics for 21 days and beclomethasone nasal spray, guaifenesin-pseudoephedrine HCl tablets, steam inhalations, and nasal saline sprays for 30 days.[27] Sinus lavage may be required to identify the organisms involved for recurring infections, but ultimately surgical intervention is often required to facilitate sinus drainage.

Referral to an Otolaryngologist

Table 3 lists the indications for referring patients with sinusitis to an otolaryngologist who can do nasal endoscopy and an antral puncture to obtain material for culture and to facilitate therapeutic irrigation. All of these patients will be evaluated by sinus CT series.

The primary surgical approach for sinusitis has shifted from the radical resection of damaged mucosa to endoscopic operations for correcting obstruction of the osteomeatal complex, allowing the sinus mucosa to heal with adequate ventilation and drainage, and thus restoring mucociliary function.[77] Indications for functional endoscopic sinus operations include medically refractory chronic sinusitis and recurrent acute sinusitis associated with abnormalities of the osteomeatal complex.[5,78,79] Structural abnormalities that can be detected include mucoceles, sinus or nasal polyps, and concha bullosa of the middle turbinate that obstructs the osteomeatal complex. Only if symptoms persist despite medical therapy and correlate with objective endoscopic and CT scan findings is surgical therapy warranted. In a group of patients with chronic sinusitis with a median one-year follow-up, 90% felt that surgical therapy lessened symptoms, with 50% having complete resolution of their symptoms.[80] Results were better in those patients in whom a substantial nasal deformity was corrected, and relief of facial pain was more common than the resolution of other symptoms. An opacified sphenoid sinus portended a poor outcome. Of this group of 155 patients, 11% required a second endoscopic operation, and 6% later required traditional surgical treatment.

In summary, community-acquired sinusitis in adults is a common problem. Diagnosis generally rests on historical and examination features. Transillumination and plain radiography are rarely used by clinicians any longer. Most patients can be managed successfully with a regimen of empiric antibiotics and oxymetazoline nasal decongestant for 10 to 14 days. Because pneumococci and *H influenzae* are the most common causal organisms, trimethoprim-sulfamethoxazole or amoxicillin-clavulanate are first-line antibiotic choices. A lack of resolution or the frequent recurrence of sinusitis despite longer-term therapy with a penicillinase-resistant antibiotic warrants evaluation with CT imaging and specialty referral.

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Outpatient Treatment of Adult Asthma

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As a chronic disease with intermittent exacerbations, asthma is treated primarily in the outpatient setting by primary care physicians. Asthma is the result of complex and only partially understood interactions of respiratory, inflammatory, and neural cells and their mediators. The goals of asthma therapy are to prevent and relieve symptoms, allow normal activities of daily living, restore and maintain normal pulmonary function, avoid adverse effects from interventions, and minimize inconvenience and cost. These goals can be achieved through educating patients, assessing and monitoring asthma severity, avoiding or controlling asthma triggers, establishing an intervention plan for routine self-management and the management of exacerbations, and providing regular follow-up care. We present a stepped approach to asthma pharmacotherapy, emphasizing anti-inflammatory therapy—inhaled corticosteroids, cromolyn sodium, or nedocromil sodium—as a summary of recent national and international recommendations.

(Kleerup EC, Tashkin DP: Outpatient treatment of adult asthma. West J Med 1995; 163:49-63)

Asthma affects about 10 million Americans and results in more than 100 million days of restricted activity.[1(p317)] Despite the availability of newer drugs for its treatment, the morbidity and mortality of asthma have increased in the United States and other countries. It is uncertain if this increase in asthma morbidity and mortality has been caused by changes in the disease, the environment, or the population; unappreciated effects of the drugs used to treat asthma; or a failure to adopt recommended optimal treatment.

Asthma is difficult to define as a disease and may represent a mixture or range of causes or mechanisms. The following is an operational definition[2(p1)]:

> Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway hyperresponsiveness to a variety of stimuli.

National panels in the United States,[3,4] Great Britain,[5,6] Canada,[7] and Australia and New Zealand[8] and an international consensus panel[2] have recently proposed guidelines for the management of asthma.* Based on a combination of facts and the best guesses of experts, they all emphasize the importance of education, self-management, inhaled anti-inflammatory agents, and self-monitoring using peak expiratory flow (PEF) measurements. The guidelines differ somewhat in the definitions of severity and permissiveness of the formulary recommended. The degree to which the guidelines have been implemented in the general care of patients with asthma remains speculative.

*See also the editorial by H. A. Boushey, MD, "Asthma Therapy—Future Promise and Current Practice," on pages 79-80 of this issue.

Cellular Processes in Asthma

The exact mechanism(s) that causes the clinical syndrome of asthma is (are) unclear. The underlying abnormality is inflammation of the airways (cellular infiltration, edema, nerve irritation, vasodilatation) resulting in bronchoconstriction (airway smooth muscle constriction), increased mucous secretions (submucosal gland and goblet cell hyperplasia and stimulation), and airway hyperresponsiveness. A number of triggers or mediators produce asthmalike responses in susceptible persons at much lower concentrations than in "normal" subjects. These stimuli may act by triggering cascades of cell activation with subsequent cytokine release, neurologic excitation with neuropeptide or neurotransmitter release, or both. Other elements act to limit the triggered responses. Medications may act to inhibit, arrest, augment, or counteract one or more elements in the cascades. The mediators and cells involved in asthma are summarized in Tables 1 and 2. Mast cells and eosinophils play a central role in asthma.[9,10] Helper T cells orchestrate the activation and recruitment of eosinophils and mast cells through cytokines (interleukins 3, 4, and 5 and granulocyte-macrophage colony-stimulating factor).[10] Important end effectors include neuropeptides, leukotriene (C_4, D_4, and E_4) products of the 5-lipoxygenase pathway, prostaglandin (PGD_2, PGE_2, PGI_2, $PGF_{2\alpha}$) and thromboxane A_2, products of the cyclooxygenase pathway, and platelet-activating factor.[11-13] The neuropeptides are regulated by selective degradation by neutral endopeptidase,

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ABBREVIATIONS USED IN TEXT

$FEF_{25\%-75\%}$ = forced expiratory flow between 25% and 75% of forced vital capacity
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
HPA = hypothalamic-pituitary-adrenal [axis]
MDI = metered-dose inhaler
PC_{20} = provocative concentration needed to produce a 20% drop
PEF = peak expiratory flow [rate]
PG = prostaglandin

chymase, and tryptase.[14-16] In experimental antigen challenge, the immediate reaction is initiated by nerves and inflammatory cells already present in the airways. The late-phase reaction (3 to 8 hours) is the result of new cellular infiltration and activation. These cells then release mediators, resulting in a second bronchospastic response. The activation of cells, particularly T-helper and mast cells, may persist long after the antigenic challenge has ended. The late-phase reaction results in an increase in airway hyperresponsiveness that may persist in a self-perpetuating manner or be reinforced with continual reexposure to antigen triggers.[17]

Pathophysiology of Asthma

Asthma is characterized by reversible airway obstruction and airway hyperresponsiveness. Spirometry reveals low forced expiratory flow rates (forced expiratory volume in 1 second [FEV_1], forced expiratory flow between 25% and 75% of forced vital capacity [$FEF_{25\%-75\%}$], and PEF rate) with normal or increased lung volumes (functional residual capacity, residual volume, and total lung capacity). The airway obstruction is partially or completely reversible spontaneously or with bronchodilators (improvement of ≥13% in FEV_1, ≥23% in $FEF_{25\%-75\%}$, and ≥20% in PEF rate).[18] The degree of obstruction varies with exacerbations, therapy, and time of day. Nonspecific triggers of bronchospasm (methacholine, histamine) induce it at much lower concentrations in patients with asthma than in those without. For example, the provocative concentration of methacholine necessary to produce a 20% drop (PC_{20}) in the FEV_1 is generally 10 mg per ml or less in patients with asthma and may range from 20 to more than 200 mg per ml in those without asthma. Patients with allergic rhinitis have intermediate airway reactivity with some overlap to both sides (5 to 50 mg per ml).

Other nonspecific triggers such as exercise and cold air can also produce an immediate bronchospastic reaction in asthmatic patients. Following antigen challenge, there is a late-phase influx and activation of inflammatory cells. This results in an increase in nonspecific hyperresponsiveness and predisposes the patient to subsequent episodes of bronchospasm. A circadian variation in cortisol and epinephrine levels, vagal tone, and inflammatory mediators results in a peak of bronchial reactivity and a nadir of the PEF rate between 4 AM and 8 AM and may account for episodes of nocturnal bronchospasm.[19]

Goals of Therapy

Therapy for asthma is directed at the underlying causes and mechanisms of the disease. At present, most forms of asthma are not "curable" but can be treated with great success. For most patients, asthma is a continual process with periodic exacerbations. Treatment must address both the underlying chronic inflammatory process and the overt symptoms apparent to the patient. The goals of therapy can be summarized as follows:

- Relieve and prevent symptoms.
- Allow normal activities of daily living including work (school) and exercise.
- Restore and maintain normal pulmonary function.
- Avoid adverse effects from interventions.
- Minimize inconvenience and cost.

For patients, asthma is manifested by the symptoms perceived. Most commonly, cough, wheezing, dyspnea, and chest tightness may be present episodically or continuously. Nocturnal symptoms or symptoms on awakening in the morning are common because of the diurnal variation of pulmonary concentrations, or responsiveness to endogenous catecholamines, vagal tone, and adrenocorticosteroids.[19] For any given patient, a particular symptom may be most prevalent or bothersome. Because of the frequently gradual onset of asthma and its long-term nature, it is not unusual for patients to ignore even serious symptoms as "normal" for them. Isolated cough is not unusual. A rapid relief of symptoms reduces the effects of the asthma on a patient and may be lifesaving. Preferable is the prevention of symptoms and particularly exacerbations manifested by more severe symptoms.

The prevention and the relief of symptoms allow asthmatic patients to participate fully in all physical and social activities. Patients with well-controlled asthma should not be restricted in their physical activity. With proper treatment, asthma should not result in excess loss of time from work or school or, indeed, from any activity. Clearly, poorly controlled asthma limits exercise capacity. Adequate therapy should relieve ventilatory limitations to exercise and prevent the occurrence of exercise-induced asthma. In rare cases, occupational asthma may not be controllable without a complete avoidance of inciting triggers in the workplace.

Patients' perceptions of asthma vary greatly. Symptoms may sometimes be present with unmeasurable physiologic changes, or conversely, pronounced declines in lung function may not cause any duress. A reversible obstructive ventilatory defect is the hallmark of asthma. With aggressive therapy, most patients' lung function will return to normal or near normal. Although a proportion of patients with severe asthma appear to have a component of fixed or permanent obstruction, they also have a large component that is responsive to therapy.

All medications are associated with possible adverse reactions. Some side effects are an extension of a drug's intended pharmacologic actions and are at times unavoidable if doses are to be adequate to control the disease.

TABLE 1.—*Mediators of Inflammation and Bronchospasm in Asthma*

*Effect**	*Mediator*	*Source*
Airway diameter—bronchoconstriction		
Decreased	Leukotrienes C_4, D_4, E_4	Mast cells and eosinophils
	Histamine potentiated by chymase	Mast cell degranulation
	C3a activation by tryptase	Mast cell degranulation
	Prostaglandin D_2	Mast cells
	Release augmented by neuropeptide Y	Adrenergic nerves
	Substance P	C-fiber sensory nerves
	Degraded by chymase	Mast cell degranulation
	Degraded by neutral endopeptidase	Type II epithelial cells, submucosal glands, nerves, and airway smooth muscle
	Augmented by inhibition of neutral endopeptidase	Viral or mycoplasmal infections, hypertonic saline inhalation, toluene diisocyanate (TDI)?
	Release augmented by neuropeptide Y	Adrenergic nerves
(proximal)	Acetylcholine	Cholinergic nerves
(peripheral)	Neurokinin A (tachykinin)	C-fiber sensory nerves
	Degraded by neutral endopeptidase	Type II epithelial cells, submucosal glands, nerves, and airway smooth muscle
	Augmented by inhibition of neutral endopeptidase endopeptidase	Viral or mycoplasmal infections, hypertonic saline inhalation, TDI?
	Augmented by platelet-activating factor (PAF)	Mast cells and eosinophils
	Neurokinin B (tachykinin)	C-fiber sensory nerves
Increased	Vasoactive intestinal peptide (VIP)	Cholinergic nerves
	Degraded by tryptase	Mast cell degranulation
(proximal)	Nitric oxide	Nonadrenergic noncholinergic nerves
Mucous secretion		
Increased	Substance P†	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Gastrin-releasing peptide (GRP)	Neuroendocrine cells in the lower airways
	Degraded by chymase	Mast cell degranulation
	VIP†	Cholinergic nerves
Vascular diameter		
Increased	VIP†; nitric oxide	Cholinergic nerves
	Substance P	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Prostaglandin D_2†	Mast cells
	Histamine	Mast cell degranulation
	Angiotensin II	
	Activation of angiotensin I by chymase	Mast cell degranulation
	Bradykinin (kallidin I)	
	Degraded by chymase	Mast cell degranulation
(arteriolar)	Calcitonin gene-related peptide	C-fiber sensory nerves
	Degraded by chymase	Mast cell degranulation
Decreased	GRP†	Neuroendocrine cells in the lower airways
(arteriolar)	Norepinephrine, neuropeptide Y	Adrenergic nerves
Vascular permeability—edema		
Increased	Substance P†	C-fiber sensory nerves
	PAF; leukotrienes C_4, D_4, E_4	Eosinophils
	Histamine†	Mast cell degranulation

*The effects given in parentheses indicate the localization of the effect.
†See previous entry for factors affecting levels or actions of mediator.

Fortunately, most of the medications used for the treatment of asthma have relatively few side effects and a high degree of safety.

Inconvenience and lack of immediate effect are the greatest impediments to any long-term therapy. Unfortunately, moderate and severe asthma requires some interventions that have no immediate effect. Daily medication regimens should be as simple as possible. Avoidance and environmental manipulations should also be designed with convenience and expedience in mind. The cost to patients and third-party payers must be a consideration. If patients cannot afford the treatment in terms of time or

TABLE 2.—*Cellular Chemotaxis and Activation in Asthma*

Cell	*Mediotor**	*Source*
Mast cell.....	Proliferation and differentiation	
	Interleukin (IL)-3	T cells (equivalent to murine Th-2 cells)
	Chemotaxis	
	Leukotriene E_4	Eosinophils
	Degranulation	
	Immunoglobulin (Ig) E cross-linking	Specific antigens
	Substance P	C-fiber sensory nerves
	Inhibited by vasoactive intestinal peptide*	Cholinergic nerves
Eosinophil.....	Chemotaxis and priming	
	IL-3, IL-5, granulocyte-macrophage colony-stimulating factor	T cells (equivalent to murine Th-2 cells)
	Platelet-activating factor (PAF), leukotriene E_4	Eosinophils
	Activation	
	IL-5	T cells (equivalent to murine Th-2 cells)
	PAF	Eosinophils
	Epidermal growth factor, C3b, IgG, IgA	
	IgE production	
	IL-4	T cells (equivalent to murine Th-2 cells)
	Degranulation	
	IgE cross-linking	Specific antigens

*See Table 1 entry for factors affecting levels or actions of mediator.

dollars, they will not take it. The cost of intervention must be weighed against the cost of poorly treated asthma.

Principles of Asthma Management

- Educate the patient.
- Assess and monitor asthma severity with objective measures of lung function.
- Avoid or control asthma triggers.
- Establish medication plans for long-term self-management.
- Proactively establish action plans for the self-management of acute exacerbations in partnership with the physician.
- Provide regular follow-up care.

Education

All outpatient asthma is ultimately managed by patients. Physicians must, in partnership with their patients, develop a flexible treatment plan to guide this self-management.[20] Contingencies for acute and chronic worsening and improvement must be addressed proactively. The plan may need to be changed over time. A large degree of autonomy may be given to patients, but the limitations of patients' ability to manage their asthma must also be firmly established. The latitude allowed patients is influenced by their knowledge, experience, confidence, and motivation. Patient autonomy does not absolve physicians from being responsive and available. Education is central to asthma self-management and includes both the transmission of information and training in skills (Table 3). Training patients in the self-management of asthma may require more initial physician time than the traditional paternalistic approach. Nurse educators can provide a valuable extension to physicians' educational efforts. Elements must be repeatedly reviewed and reinforced. Time must also be allotted for patients to ask questions and to express their expectations and concerns.

To understand the elements of self-management, patients require a fundamental understanding of the characteristics and causes of asthma. An explanation of the inflammatory nature of asthma is important to their understanding of the basis for the pharmacologic and nonpharmacologic interventions. Patients must understand the role of different medications in reducing inflammation and relieving bronchospasm. Patients need skill in the use of metered-dose inhalers (MDIs) and PEF meters to effectively self-manage their asthma. Physicians must also address fears regarding medications and, in particular, corticosteroids.

Patients do not have asthma in isolation. Physicians must facilitate the understanding and support of a patient's family and supervisors or teachers at work or school. This process may entail discussions with parents, spouses, supervisors, teachers, athletic coaches, and school or work health professionals. It also includes liai-

TABLE 3.—*Sample Plan for Patient Education*

Knowledge	*Skills*	*Physicion Interventions*
Disease process		
Inflammation, bronchospasm, hypersensitivity		Diagnosis, assess severity, set goals of therapy
Controlling asthma triggers		
Allergens, other environmental, occupational, psychological, medications, foods	Dust proofing, panic control, stress reduction, coping skills, dietary limitations	Identify triggers
Drug therapy		
Anti-inflammatory agents, β_2-agonists, oral corticosteroids, other medications	Inhaler technique, use of spacers, nebulizers, special delivery devices, cleaning devices	Stepped therapy
Monitoring		
Peak flow, warning signs	Peak expiratory flow (PEF) meter and diary	Personal best or predicted PEF rate, green, yellow, and red zones
Management		
Treatment of exacerbations		Exacerbation treatment protocol
Complicating factors		
Sinus disease, gastro-esophageal reflux, ABPA		Identification and treatment
Special topics		
Exercise, fitness, sex		

ABPA = allergic bronchopulmonary aspergillosis

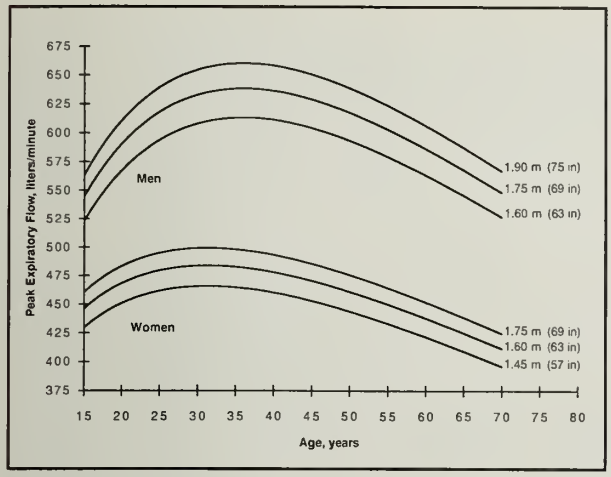

Figure 1.—Predicted normal rates are shown for peak expiratory flow. The lower 90% confidence interval (below which only 5% of the values from normal subjects would be expected to fall) is 70 to 80 liters/minute below the predicted peak expiratory flow (from Nunn and Gregg[26]).

son with other health professionals—specialists, primary care physicians, ancillary services—caring for a patient. Patients may also benefit from community support groups, which can be identified through local branches of the American Lung Association.

The control of asthma is a long-term endeavor for both patients and physicians. Feedback and measurements of progress help retain interest and enthusiasm and facilitate adjustments to management. Symptoms are most important to patients, but the importance of any particular symptom varies from patient to patient. It is useful to identify symptoms or asthma-provoking activities that are important to a particular patient and to review the response to therapy in the lessening of those specific symptoms and improved activity levels. Ultimately, symptoms are an imprecise assessment and subject to many confounding factors. Objective measurements of response are critical to assessing control. Peak expiratory flow rate monitoring is the most useful. Inexpensive and reliable, it can be performed by patients at frequent intervals to detect asymptomatic declines or improvements in lung function. Results can be compared with patients' historical best or with sex-, age-, and height-adjusted normal values (Figure 1).

Assessment of Severity

The first step in developing a plan for managing asthma is to assess the severity of the disease. Severity can be classified by clinical pattern, symptoms, need for medications and medical interventions, and severity of airflow obstruction (Table 4). These indicators of severity (or worsening of control) may not vary in concert with one another. A particular patient's disease may rank moderate in one category and mild in another. Patients with a previous near-fatal episode of asthma have a marked decrease in the perception of airway resistance (an altered sense of dyspnea). Patients with less severe asthma also have a reduced perception of dyspnea, but overlap considerably with normal subjects.[21] There is little information regarding the comparative sensitivity of these measures for detecting exacerbations, but typically for any patient an exacerbation will occur in a reproducible pattern—increased frequency of nocturnal awakenings, followed by a fall in the PEF rate, followed by increased cough, wheeze, chest tightness, or shortness of breath, followed by an increased use of inhaled albuterol. Unfortunately, patients and physicians often underestimate the degree of severity of asthma. This may lead to undertreatment and increased morbidity and mortality.

In general, previous episodes of severe asthma portend future episodes of severe asthma and increased morbidity and mortality. The recognition of risk factors for morbidity and mortality should prompt close and aggressive management. Previous life-threatening exacerbations of acute asthma resulting in respiratory failure, as evidenced by respiratory acidosis, intubation, or both, are most important.[22] Any hospital admission for asthma within the past year, particularly while the patient is receiving long-term oral corticosteroids, is an important risk factor. A number of demographic risk factors have been identified, including age (late teens to early 20s), race (African American), and socioeconomic status (inner-city, low-income). Although asthma is not caused by emotion, the following psychological factors may affect its severity and treatment: depression, alcohol abuse, recent family loss and disruption, recent unemployment, and personality disorders.[23] Barriers or lack of access to medical care, whether due to economic, social, cultural, or psychological factors, affect the control of asthma. Other risk factors that need to be assessed include noncompliance with maintenance anti-inflammatory therapy and avoidance measures, dependence on high doses or the frequent use of β_2-agonists, and recent reductions in or withdrawal from corticosteroids or other anti-inflammatory medications.

The nature and severity of symptoms reflect the severity of asthma in general. An increase in symptoms and acute exacerbations represents episodic worsening of asthma in response to exogenous stimuli—irritants, allergens, exercise, infection—or without identifiable provocation. Cough, chest tightness, wheezing, and breathlessness (with or without exercise) are common complaints. The frequency and duration ranges from rare to continual. It is important to elicit a history regarding nocturnal symptoms, awakenings from sleep, and early morning wheezing. Diurnal variability leads to increased susceptibility in the early morning. Symptoms may be induced by or present with or following exercise and result in dramatic exercise intolerance and avoidance. An important measure of asthma severity is time lost from or diminished effectiveness at work or school. Patients with more than rare absences have inadequately controlled asthma or more severe disease than previously appreciated.

The level of treatment necessary to maintain good control is another index of asthma severity. Patients with

TABLE 4.—*Assessment of Asthma Severity**

Indicator	Asthma Severity: Very Mild	Mild to Moderate	Moderate to Severe	Severe
Symptoms				
Cough, wheezing, or both	Intermittent and brief ≤2×/wk	1-2 episodes/day	4-6 episodes/day	Nearly continuous
Nocturnal asthma	≤2×/mo	2-3×/wk	Nearly nightly	Nightly
Exercise tolerance	Nearly normal	Slightly diminished	Diminished	Marked limitation
Work or school attendance	Unaffected	Occasionally affected	Substantially affected	Greatly affected
Least symptomatic days	Few clinical signs or symptoms of asthma between exacerbations	Occasional to frequent cough, wheezing, or both	Cough and low-grade wheezing often present	Cough and wheezing usually present
Treatment				
Therapy necessary to maintain control	Periodic use of bronchodilators as needed	Continuous inhaled anti-inflammatory therapy: low-dose inhaled corticosteroids, cromolyn sodium, or nedocromil sodium; occasional bursts of oral corticosteroids	Continuous inhaled anti-inflammatory therapy (usually high-dose with or without nedocromil), more frequent bursts of oral corticosteroids, may need around-the-clock bronchodilators	Continuous high-dose inhaled corticosteroids, frequent bursts of oral corticosteroids, often need around-the-clock bronchodilators, may need alternate-day or daily oral corticosteroids
Urgent treatments at MD's office or ED	Rare	<3×/yr	≥3×/yr	
Hospital admissions	None	Infrequent	≥2×/yr or requiring intubation	
Pulmonary function				
Peak expiratory flow (PEF) rate	>80% of predicted	60% to 80% of predicted	<60% of predicted	
PEF variability	<20%	20% to 30%	>30%	
Spirometry	FEV_1/FVC ratio >80%	FEV_1/FVC ratio 50% to 80%	FEV_1/FVC ratio <50%	
Response to bronchodilator	≥15% improvement in FEV_1, usually relieving any mild obstruction	≥15% improvement in FEV_1, usually to normal or near normal	≥15% improvement in FEV_1, but generally not to normal	
Methacholine sensitivity	PC_{20} 5 to 10 mg/ml	PC_{20} 1 to 5 mg/ml	PC_{20} <1 mg/ml	

ED = emergency department, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MD = physician, PC_{20} = provocative concentration needed to produce a 20% drop in FEV_1

*Modified from Sheffer,[2,3] British Thoracic Society et al,[5,6] Hargreave et al,[7] and Woolcock et al.[8] This table is a composite of national and international asthma severity grading schemes. Patients may have different degrees of severity in different categories. Select the highest level of severity as the basis for therapy.

more severe asthma require more therapy to gain and retain control. The assessment of past therapies must include medications (dose, duration, and compliance) and effectiveness (symptoms and objective measures). Whereas patients may report that β_2-agonists provide short-term relief of symptoms, their asthma may remain poorly controlled in terms of objective measures, such as the PEF rate, PEF variability, FEV_1/FVC ratio, and PC_{20}.

Monitoring of the PEF rate should be seriously considered in patients who take medications daily (moderate to severe asthma). In patients with mild asthma, it is less likely that PEF monitoring will result in a substantial reduction in morbidity or mortality.[24,25] During the adjusting of medications, patients should record the best of three PEF rates in the morning and evening at consistent times. If bronchodilators are used, PEF rates should be recorded at least before and optimally after (10 to 15 minutes) inhaling bronchodilators. After good control has been established, it may be more convenient to record only the best daily morning PEF rate. This strategy allows contin-

TABLE 5.—*Zone System of Peak Expiratory Flow (PEF) Monitoring*

Zone	*Interpretation*	*Best PEF Rate, %*	*AM/PM PEF Variability, %*
Green	All clear	>80	<20
Yellow	Caution	50-80	20-30
Red	Alert	<50	>30

ued early detection of asymptomatic declines in lung function that may indicate impending exacerbation or a decline in the degree of control. As evidence of good control, PEF values should be near a patient's best and near population normal values. The zone system (Table 5), analogous to the traffic light, has been developed to grade changes in PEF rates. A decline into the yellow zone may indicate the beginning of an acute exacerbation or ongoing deterioration. Therapy may be changed to increase the dose of anti-inflammatory inhalers or add a "burst" of oral corticosteroids (discussed later). Descent into the red zone indicates severe deterioration and may require emergency intervention from the physician or in the hospital emergency department. The zones are approximations and need to be tailored to each patient based on his or her history and past response to therapy. Ideally, personal best PEF rates are near population normals (see Figure 1)[26]:

Men:

$$\log_e \text{PEF (liters/min)} = 0.544 \log_e \text{Age} - 0.0151 \text{ Age} - 74.7/\text{height (cm)} + 5.48$$

Women:

$$\log_e \text{PEF (liters/min)} = 0.376 \log_e \text{Age} - 0.0120 \text{ Age} - 58.8/\text{height (cm)} + 5.63$$

Peak expiratory flow rates vary with the time of day, with the lowest values being in the morning hours (8 to 10 AM) and the highest in the afternoon (3 to 5 PM). Normal variability is probably less than 10% (4% to 18%), but may be greater than 25% (6% to 27%) in patients with stable asthma. Following an episode of asthma exacerbation, the PEF rate variability may be more than 50%.[27] The degree of PEF rate variability correlates with FEV_1 variability, the severity of asthma, and airway hypersensitivity:

$$\text{PEF Variability} = \left| \frac{\text{AM PEF} - \text{PM PEF}}{(\text{AM PEF} + \text{PM PEF}) / 2} \right|$$

Control of Asthma Triggers

Nonpharmacologic interventions should be considered in all patients being treated for asthma. In some patients, specific environmental triggers of asthma can be identified (Table 6) and avoided (Table 7). The extent to which this is possible varies from patient to patient. The simplest approach is a careful history. Patients will often associate worsening symptoms with certain activities, locations, or seasons. The ability to avoid triggers varies depending on the nature and prevalence of the trigger. The avoidance of triggers such as dust mites for two to nine months may result in a decrease in symptoms, medication use, and specific and nonspecific bronchial hyperresponsiveness.[28-30] The value of skin testing is limited without an accompanying history of a substantial response on exposure. Inhalation challenge with specific antigens is possible in some cases, but should be done only by a specialist and usually is relevant only in a research setting.

TABLE 6.—*Asthma Triggers—Inducers of Inflammation, Bronchospasm, or Both*

- Respiratory viruses
- Occupational sensitizers
  - Toluene diisocyanate, western red cedar (*Thuja plicata*) sawdust, grain dust, cotton bract
- Allergens
  - Indoors
    - House dust mites, cockroaches, pets (cats more than dogs), feathers or down, molds
  - Outdoors
    - Pollens—grasses, trees, molds
- Food additives
  - Metabisulfite
- Medications
  - Aspirin (10% to 30% of persons with asthma)
  - Other nonsteroidal anti-inflammatory drugs
  - β-Blockers (including eyedrops)
- Environmental
  - Ozone, sulfur dioxide, smog
  - Cigarette smoke, including secondhand smoke
  - Fine aerosols—household sprays, fog
  - Cold air, exercise
- Extreme emotion

Pharmacologic Therapy

Pharmacologic therapy for asthma can be divided into two broad categories: anti-inflammatory drugs and bronchodilators. Patients with mild asthma require an inhaled

TABLE 7.—*Environmental Control of Asthma*

Trigger	*Control*
Dust or dust mites.....	Wash bedding in hot water (58°C [137°F]) Cover mattresses and pillow cases Remove carpets from bedrooms Use acaricides or denaturing agents (tannic acid) Replace upholstered furniture and draperies Adjust humidity to <50% Filter air with high-efficiency particulate air cleaners
Molds.....	Provide adequate ventilation Clean bathrooms carefully and frequently Limit the number of houseplants Clean walls and add mold inhibitor to paint Reduce humidity to <35%
Cats.....	Keep cat out of bedroom Wash cat 3×/wk, then every 2 to 3 wk Use denaturant (tannic acid) on carpets Give cat away

TABLE 8.—*Strength and Dosage of Anti-inflammatory Medications*

Drug, μg/puff	Strength/ puff*	Manufacturer's Recommended Dose, puffs/doy		Beginning of HPA Axis Suppression, puffs/day†
		Starting	Maximum	
Beclomethasone dipropionate, 42 ..	1	6-8	20	24-30
Triamcinolone acetonide, 100....	1.5-2	6-8	16†	16-20
Flunisolide, 250	2.5-3	4	8†	10-12
Cromolyn sodium, 800.....	<1	8	8	NA
Nedocromil sodium, 1,750	<1	8	8	NA

HPA = hypothalamic-pituitary-adrenal, NA = not applicable

*Approximate potency/puff based on limited data (from Grandgeorge et al[31]).
†May be exceeded in patients not responding adequately to lower doses.

β_2-agonist only on an as-needed basis for the relief of infrequent symptoms. They may also benefit from prophylactic therapy with a β_2-agonist, cromolyn sodium, or nedocromil sodium before exercise or an anticipated exposure to another asthma trigger. For patients with more frequent symptoms or more substantial lung function abnormality, the mainstay of asthma therapy is anti-inflammatory medication—inhaled corticosteroids, cromolyn, or nedocromil. Anti-inflammatory agents, administered on a regularly scheduled basis, treat the underlying inflammation of asthma, reducing the airway hyperreactivity and decreasing the frequency of bronchospasm and symptoms, whereas bronchodilators provide a rapid, effective relief of bronchospastic symptoms—wheezing, chest tightness, or dyspnea.

Inhaled Anti-inflammatory Agents

Airway inflammation is present even in patients with asymptomatic asthma, and the amount correlates with disease severity. Inhaled corticosteroids are nonspecific suppressors of inflammation.[3] They inhibit arachidonic acid metabolism, resulting in the decreased production of leukotrienes and prostaglandins. They also reduce the migration and activation of inflammatory cells by inhibiting cytokine production. In addition, inhaled corticosteroids increase the responsiveness of the β-receptors of the airway smooth muscle. The result is a decreased frequency of acute exacerbations, symptoms, and the need for concurrent medications. Diurnal variability in PEF rates and airway responsiveness to methacholine also decrease. Three inhaled corticosteroid preparations are currently available in the United States: beclomethasone dipropionate (Beclovent, Vanceril), 42 μg per puff; triamcinolone acetonide (Azmacort), 100 μg per puff; and flunisolide (AeroBid), 250 μg per puff (Table 8).[31]

Detectable suppression of the hypothalamic-pituitary-adrenal (HPA) axis is uncommon at doses below 1,000 to 1,500 μg (24 to 30 puffs per day) of beclomethasone or its equivalent (triamcinolone, 16 to 20 puffs per day; flunisolide, 10 to 12 puffs per day). In patients with moderate asthma, relatively low doses of inhaled corticosteroids (such as 8 puffs of beclomethasone per day or its equivalent) are usually sufficient for satisfactory asthma control. In patients with severe asthma, however, higher doses are required, and manufacturers' recommended doses are often exceeded.[32] Doses as high as 2,000 μg per day of beclomethasone (or its equivalent) have been used successfully. The optimal dose of inhaled corticosteroids is that which effectively controls asthma. Even if HPA axis suppression is present, the degree of suppression is less than that caused by a daily regimen of oral prednisone that produces a comparable control of asthma.[33] Localized infections with *Candida albicans* may occur in the mouth, pharynx, or occasionally the larynx. Clinically important infection may be treated with antifungal agents and the discontinuation of the inhaled corticosteroid. The incidence of local oral effects may be reduced by the use of a spacer and rinsing the mouth following use. Cough due to the additive oleic acid may occur with the use of Beclovent or Vanceril, but is minimized by the use of spacers. Reversible dysphonia can occur with deposition of the drugs on the vocal cords. Dermal thinning and purpura may occur particularly in older patients.[34] Laboratory studies indicate that the use of inhaled corticosteroids in high doses (≥1,500 μg of beclomethasone or its equivalent) may decrease bone density, but the implication of these small-scale findings with respect to the risk of fractures is unclear. Results in patients are less clear. Inhaled corticosteroids may also cause nausea, vomiting, diarrhea, headache, and sore throat. Patients with unstable or severe disease may benefit from three- or four-times-a-day dosing. Stable patients with mild or moderate asthma, however, may have improved compliance and equivalent effectiveness with twice-a-day dosing. Frequent exacerbations indicate a failure of the regimen and are an indication to intensify the long-term therapy.

Before increasing inhaled corticosteroid doses, it is important to review inhaler technique and compliance. In one study, 45% of patients were estimated to be taking less than 51% of the prescribed doses of inhaled corticosteroids.[35] After asthma control is achieved, a stepwise decrease in anti-inflammatory therapy may be possible and is advisable. In a recent Finnish study, 74% of patients with mild asthma remained stable after a two-thirds reduction in the dose of inhaled corticosteroids after two years at the higher dose.[36] The ideal dose of inhaled corticosteroids is the minimum dose necessary to achieve and maintain the goals of therapy.

Cromolyn and nedocromil are nonsteroidal but less potent anti-inflammatory agents (see Table 8). Cromolyn inhibits mediator (histamine) release and degranulation from mast cells. It also may possess tachykinin (substance P and neurokinin B) antagonist properties.[37] Nedocromil inhibits the release of histamine and PGD_2 from mast cells[38] and the mobilization of neutrophils and eosinophils.[39] Nedocromil also inhibits neural impulse propagation in the sensory C fibers of the airway wall, resulting in decreased neuropeptide release.[40] It has a greater protective effect than cromolyn against bron-

chospasm induced by nonallergenic stimuli, such as cold air, sulfur dioxide, metabisulfite, and hypertonic saline solution.[41] Cromolyn sodium (Intal) is available as an MDI delivering 800 μg per puff (as well as a dry-powder inhaler and a solution for use with a powered nebulizer). Nedocromil sodium (Tilade) is available as an MDI delivering 1.75 mg a puff. Nedocromil may be slightly more effective than cromolyn.[42] Nedocromil (2 puffs 4 times a day) is about equivalent to beclomethasone (2 puffs 4 times a day).

Because both nedocromil and cromolyn have favorable side-effect profiles and no HPA axis suppression, they should be considered for use in patients with mild to moderate asthma. No studies have been done of the effectiveness of higher doses. If asthma control has been achieved, a reduction in the frequency of dosing from four to three or two times a day may be attempted several weeks after the initiation of therapy. Prophylactic dosing with cromolyn or nedocromil is also useful to prevent symptoms induced by exercise or trigger exposure; however, inhaled β_2-agonists are more effective for the prevention of exercise-induced bronchospasm. Concomitant therapy with nedocromil and inhaled corticosteroids may permit a reduction in the dose of inhaled corticosteroids in patients requiring high doses of the latter.[43] Nedocromil and cromolyn are generally well tolerated, but occasionally their use is associated with gastrointestinal symptoms (nausea, vomiting, dyspepsia, or abdominal pain) more often than is placebo. An unpleasant taste, throat irritation, or dryness may also result in discontinuation or poor compliance. Intal (cromolyn) infrequently causes reproducible bronchospasm, nasal congestion, cough, or laryngeal edema.

Oral Anti-inflammatory Agents

Oral corticosteroid therapy can be divided into two types—"burst" and long-term (ongoing). Burst regimens of 7 to 14 days are appropriate for acute exacerbations and poorly controlled chronic asthma, either at the initiation of therapy or when the response to long-term anti-inflammatory therapy is inadequate. Little residual effect on the HPA axis occurs after burst therapy, and tapering is not necessary to prevent adrenal insufficiency. During a burst regimen, however, it is often useful to taper the corticosteroid dose to evaluate the effect of withdrawal on a patient's asthma. Gradual withdrawal allows the early detection of a relapse of asthma symptoms or objective declines in airflow without catastrophic exacerbations.

The following is an example of a burst regimen: prednisone each morning: 60 mg on days 1 to 3, 50 mg on day 4, 40 mg on day 5, 30 mg on day 6, 20 mg on day 7, 10 mg on day 8, and stop (dispense 33 tablets, 10 mg each). Divided doses (two thirds in the morning, one third in the evening) may be used with daily doses of more than 30 mg. In general, the requirement for a prednisone burst necessitates a temporary or long-standing increase of a patient's inhaled anti-inflammatory regimen. Every effort should be made to minimize the long-term use of oral corticosteroids. For an equivalent degree of asthma control, the daily use of oral corticosteroids causes considerably more systemic side effects than a daily use of inhaled corticosteroids. Continual efforts should be made to reduce oral corticosteroid doses by increasing the dose of inhaled corticosteroids. Patients without satisfactory control of their asthma who are taking more than 10 mg of prednisone daily or 20 mg every other day should be referred to a specialist with this explicit goal. In patients previously on long-term maintenance therapy with oral corticosteroids, the withdrawal of oral corticosteroids may result in adrenal insufficiency for as long as a year. This complication is not prevented by the use of inhaled corticosteroids. During adrenocortical stress, including that caused by surgical therapy, oral corticosteroid therapy may be necessary to prevent symptomatic hypoadrenalism.

Bronchodilators

The major role of bronchodilators is the temporary relief of symptoms primarily due to bronchoconstriction. Regularly scheduled, around-the-clock use of short-acting or long-acting bronchodilators may mask the severity of asthma, resulting in undertreatment of the underlying inflammation.

Short-acting selective β_2-agonists are ideal for the initial control of bronchospasm and the prevention of exercise-induced bronchospasm. Such agents include albuterol sulfate (Proventil, Ventolin), terbutaline sulfate (Brethaire), metaproterenol sulfate (Alupent), bitolterol mesylate (Tornalate), and pirbuterol acetate (Maxair), all available as MDIs. For mild symptoms, two puffs as needed should be sufficient. Frequent use indicates a more serious exacerbation or poor control. When used in higher doses, all "selective" β_2-agonists will exhibit β_1-agonist effects, most often manifested by tachycardia in addition to tremor or anxiety (both β_2-agonist effects). Less selective β-agonists (epinephrine bitartrate [Primatene], isoproterenol [Isuprel] hydrochloride, and isoetharine mesylate [Bronkometer]) may cause a higher degree of cardiac side effects. In large doses, the use of inhaled β_2-agonists may result in a slight lowering of the serum potassium level.

Ultralong-acting bronchodilators—such as salmeterol xinafoate (Serevent) (a recently released, ultralong-acting inhaled β_2-agonist with a ≥12-hour duration of bronchodilation), controlled-release oral albuterol, and theophylline—all relieve bronchospasm for extended periods of time. Their role in ongoing therapy for asthma is unclear. In patients with mild disease, they may mask an increasing severity of symptoms that would be more appropriately treated with inhaled anti-inflammatory agents. In patients with poorly controlled moderate or severe disease, they may lull the patient and physician into accepting less-than-optimal anti-inflammatory therapy. Nonetheless, around-the-clock bronchodilator therapy may be required in addition to maximal doses of inhaled corticosteroids (with or without nedocromil) for the adequate control of symptoms in patients with moderate to severe asthma. Ultralong-acting bronchodilators (sus-

tained-release theophylline or twice-a-day salmeterol inhaler) provide more consistent around-the-clock bronchodilation than regularly scheduled (4 times a day or every 4 hours), short-acting β_2-agonists such as albuterol and may be more effective in preventing nocturnal asthma symptoms.[44,45] Salmeterol also has a long duration (≥8 hours) of protection against exercise-induced bronchospasm. In some physically active young patients with mild asthma who frequently have exercise-induced bronchospasm, salmeterol taken in the morning may provide superior prophylaxis over repeated doses of a short-acting β_2-agonist before each period of exercise.

Inhaled ipratropium bromide (Atrovent) is a second-line choice for acute bronchodilator therapy in patients with asthma who are intolerant of side effects associated with β_2-agonist therapy. The onset of action is somewhat slower (peak response, 20 to 30 minutes; 50% of maximal response, 3 to 4 minutes) than that of a β_2-agonist. The quaternary ammonium structure results in poor absorption and almost no systemic atropinelike effects. It is unclear if the maximal response achieved after a high dose of a β_2-agonist or ipratropium or the combination of the two is greater. In general, however, two puffs of either a β_2-agonist or ipratropium give a submaximal response, and further improvement may be seen with an additional dose of either the same drug or the other drug. Ipratropium may produce dry mouth and a bad taste. A closed-mouth technique is recommended for the MDI to prevent spray in the eyes, causing temporary blurring of the vision.

Theophylline and Aminophylline

With the emphasis on anti-inflammatory drugs for ongoing asthma therapy and fast-acting inhaled β_2-agonists for initial treatment, theophylline has been relegated to a minor role in the treatment of asthma. Theophylline does not provide notable anti-inflammatory effects in tolerable pharmacologic doses. Superior bronchodilation is provided by β_2-agonists or anticholinergics without the attendant side effects. In acute asthma exacerbations, the addition of intravenous aminophylline to treatment with an inhaled β_2-agonist and intravenous corticosteroids increases the risk of side effects but does not improve objective measures of airflow. Adverse effects from theophylline may be seen at therapeutic levels (8 to 15 μg per ml), and severe side effects are common at higher levels. Adverse effects include nausea, vomiting, dyspepsia and gastroesophageal reflux, diarrhea, intestinal bleeding, aspiration, tachycardia, insomnia, headaches, irritability, life-threatening arrhythmias, seizures, cardiac arrest, and death. Interindividual and intraindividual variations in metabolism and absorption of theophylline are complicated by interactions with common drugs. Clearance is increased by the addition of phenobarbital, phenytoin, intravenous β-agonist (albuterol sulfate, isoproterenol), furosemide, and cigarette or marijuana smoking. Clearance is reduced with the use of erythromycin, quinolones, isoniazid, cimetidine, calcium channel blockers, allopurinol, oral contraceptives, caffeine, and influenza vaccine and with the presence of liver disease, congestive heart failure, fever, or pregnancy. The narrow therapeutic window necessitates careful monitoring, including serum theophylline levels. If theophylline is used at all, objective evidence of benefit must be shown beyond that achieved with primary lines of treatment in any patient.

Delivery Systems

Various delivery systems are available for asthma medications (Table 9). Inhalation is the preferred route because it delivers high concentrations of a drug directly to the airways, thus minimizing systemic effects for equivalent airway effects. Adjuncts such as spacers further reduce the systemic absorption and local side effects by reducing oropharyngeal deposition. With spacers, larger particles that would usually affect the oropharynx affect the spacer, and the smaller respirable particles (≤5 μm median aerodynamic diameter) slow in velocity, resulting in less throat irritation. The standard MDI requires some training and hand-breath coordination to use effectively. Patients who are extremely dyspneic, with arthritic hands, or with poor hand-breath coordination may have particular difficulties. They may benefit from the use of breath-activated MDIs (pirbuterol [Maxair Autohaler]), dry-powder inhalers, or inhalation solutions by nebulizer. Long-acting oral or inhaled bronchodilator therapy may be useful in patients with severe asthma for the control of symptoms not relieved by intensive anti-inflammatory therapy. Subcutaneous and intravenous bronchodilator preparations are potentially useful in the treatment of patients with acute exacerbations in an emergency department or hospital, but they are impractical for ongoing care.

Immunotherapy

In contrast to its efficacy in allergic rhinitis, the role of immunotherapy in asthma is unclear. In carefully selected cases, a few specific well-defined antigens (grass pollen, house dust mite, *Alternaria* species) may provide an antigen-specific reduction in sensitivity. This mild benefit must be weighed against the potential for systemic reactions (5% to 30%), including anaphylaxis, and the cost and inconvenience of weekly physician visits.[46,47]

Experimental Anti-inflammatory Therapy

The goal of the use of most experimental anti-inflammatory agents is to reduce the dependence on oral corticosteroids, particularly in patients requiring treatment with high doses of oral prednisone (>10 mg per day or 20 mg every other day) and maximal doses of inhaled corticosteroids. Troleandomycin, methotrexate, gold salts, and cyclosporine have all been studied.[48]

Troleandomycin, a macrolide antibiotic, prolongs the elimination of methylprednisolone sodium succinate. Although the dose of methylprednisolone may be reduced, the corticosteroid-associated side effects are not attenuated, at least initially.[49] A few open-label studies have shown that some troleandomycin-responsive patients

TABLE 9.—*Available Preparations of Selected Asthma Medications*

Drug	Metered-dose Inhaler (MDI)	Breath-activated MDI	Dry Powder Inhaler	Inhalation Solution	Oral	Oral Controlled Release	Sub-cutaneous	Intra-venous
Beclomethasone dipropionate	X	--	--	--	--	--	--	--
Triamcinolone acetone	X	--	--	--	--	--	--	--
Flunisolide	X	--	--	--	--	--	--	--
Cromolyn sodium	X	--	X	X	--	--	--	--
Nedocromil sodium	X	--	--	--	--	--	--	--
Bronchodilators								
Epinephrine	X	--	--	--	--	--	X	--
Albuterol	X	--	X	X	X	X	--	--
Terbutaline	X	--	--	--	X	--	X	--
Metaproterenol	X	--	--	X	X	--	--	--
Bitolterol	X	--	--	X	--	--	--	--
Pirbuterol	X	X	--	--	--	--	--	--
Theophylline or aminophylline	--	--	--	--	X	X	--	X

subsequently may achieve acceptable control of asthma symptoms and the resolution of cushingoid features with relatively low doses of alternate-day methylprednisolone,[50] although a recent double-blind, placebo-controlled study failed to show any benefit.[51]

Methotrexate, a folic acid analogue, inhibits thymidylate synthesis, resulting in an antiproliferative effect. It appears to inhibit interleukin 1 production, histamine release from basophils, and neutrophil chemotaxis by C5a and leukotriene B_4. Recent studies have demonstrated no significant difference between methotrexate use and that of placebo in reducing oral corticosteroid dosage.[51,52] It is possible, however, that a small subset of patients responds to the use of methotrexate.[52] Mild side effects include nausea, diarrhea, headache, rash, and elevated liver enzyme levels (as much as 40% of patients). Severe side effects include liver fibrosis (as much as 5%), methotrexate pneumonitis or fibrosis (3% to 5%), and opportunistic infections.

Gold salts appear to inhibit the release of histamine and leukotriene C_4 from mast cells and basophils and appear to have a range of other immunosuppressive effects. Studies are plagued by withdrawals due to side effects, but other patients often show a slight reduction in corticosteroid use.[53-55] The side effects are common (20% to 37%) and include proteinuria, dermatitis, stomatitis, nausea, and diarrhea.

Cyclosporine prevents mast cell degranulation and inhibits the transcription of interleukins 2, 3, 4, and 5 and T-cell activation. The addition of cyclosporine to a regimen of steroid-dependent asthma appears to improve PEF rates and FEV_1 values and to reduce exacerbations compared with placebo.[56] This drug has not been well studied for its steroid-sparing effect. Side effects include nephrotoxicity, hypertrichosis, paresthesias, headaches, hypertension, and herpes zoster.

Frequent monitoring and intensive intervention, especially with inhaled corticosteroids, are often effective in reducing the dose of oral corticosteroids, as evidenced by the pronounced response to placebo in studies of alternative anti-inflammatory agents. The use of experimental anti-inflammatory agents currently can only be recommended in rare cases after exhaustive attempts have been made to reduce oral corticosteroid doses using inhaled corticosteroids in maximal doses and other conventional therapies.

Stepped Therapy

The initiation of therapy must be individually tailored depending on the disease severity (Figure 2). Following the initiation of treatment at a level appropriate for a patient's severity, stepwise increases or decreases in therapy may be indicated. The presence of signs, symptoms, or abnormalities of objective measures of lung function (PEF rate, PEF variability, or spirometry) may indicate a need to initiate or increase anti-inflammatory therapy. A good clinical response and normal or near-normal objective measures of lung function may allow reductions in anti-inflammatory therapy. In patients with moderate to severe asthma, initial treatment appropriate for an acute exacerbation followed by aggressive initial maintenance therapy and gradual increments or reductions in therapy as tolerated is appropriate. In more mild cases, initial low-dose maintenance therapy may be instituted, followed by gradual stepwise increases or decrements as appropriate. Patients with mild asthma may also use a short-acting β_2-agonist (or cromolyn or nedocromil) as prophylaxis before exercise or anticipated exposure to asthma triggers. In selected cases of severe asthma, around-the-clock bronchodilators (short- or preferably long-acting oral or inhaled β_2-agonists or sustained-release theophylline) may be necessary to control frequently recurring symp-

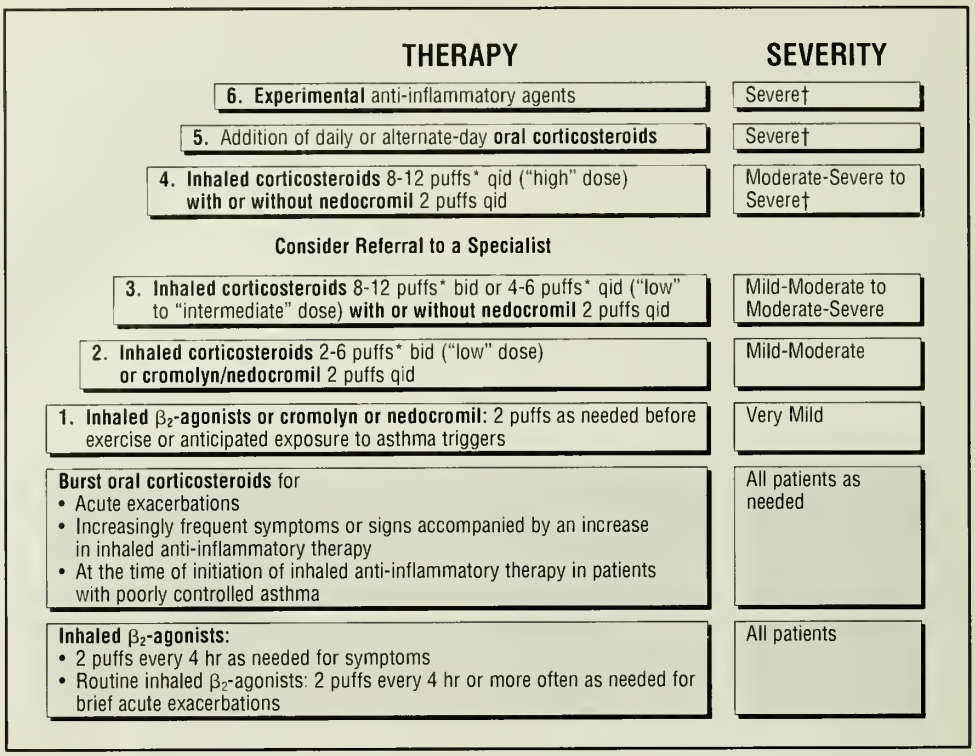

Figure 2.—Stepped therapy for asthma is shown: As asthma increases in severity, patients proceed up the steps from 1 to 6. With improvement, decreases in therapy may be possible and should be attempted on a regular basis (from Sheffer,[2,3] British Thoracic Society,[5,6] Hargreave et al,[7] and Woolcock et al[8]). *Doses of inhaled corticosteroids are given in terms of beclomethasone dipropionate: 2.5 to 3 puffs of beclomethasone are approximately equivalent to 1.5 to 2.5 puffs of triamcinolone acetonide or 1 puff of flunisolide. †Patients with severe asthma may require around-the-clock maintenance bronchodilators to control symptoms, preferably either a sustained-release oral bronchodilator (theophylline or albuterol) or an ultralong-acting inhaled bronchodilator (salmeterol). bid = twice a day, qid = 4 times a day

toms, especially nocturnal symptoms, that persist despite maximal anti-inflammatory therapy. Patients should always have medications available for the treatment of acute exacerbations, usually a short-acting β_2-agonist (which may be used at frequent intervals, if necessary, during the exacerbation) and oral prednisone. Asthma in adults will often continue to be present to a greater or lesser extent for life. Constant vigilance is required for both the recognition of deteriorating control of asthma and opportunities for reducing pharmacologic therapy when the disease is well controlled.

Acute Exacerbations

Acute exacerbations represent either the failure of ongoing therapy, the effects of intercurrent viral upper respiratory tract infections, or unexpected exposure to patient-specific triggers of asthma. Patients must be given clear guidelines—preferably in writing—for both the assessment and treatment of acute exacerbations and, in particular, when to seek a higher level of care such as a hospital emergency department. The goals for the evaluation and treatment of acute exacerbations can be summarized as follows:

- Assess the severity of an exacerbation.
- Relieve symptoms.
- Restore lung function.
- Prevent recurrence.

Patient guidelines for assessing the severity of exacerbation must be individually tailored. The first indication of an exacerbation is usually either an increase in symptoms or a decline in the PEF rate below the patient's "normal" range. The zone system (see Table 5) uses the PEF rate to provide an objective measurement of exacerbation severity. Exacerbations identified earlier, in the "yellow" range, are more easily treated. Well-instructed patients may treat many exacerbations at home alone or in consultation with their physicians. Patients should seek evaluation and treatment in an emergency department if an attack is characterized by any of the following:

- Rapid onset.
- Previous history of severe attacks.
- Peak expiratory flow rate less than 50%.
- Lack of response to initial therapy.

The pharmacologic treatment of acute exacerbations is an intensification of long-term bronchodilator and anti-inflammatory therapy. Initial therapy with a short-acting β_2-agonist such as albuterol is directed at the rapid relief of bronchospasm. An example is two to four puffs of al-

buterol every 20 minutes for three doses. This is followed by regular, around-the-clock use of β_2-agonists every three to six hours for as long as two days or until the episode resolves. A lack of appropriate response is indicated if the initial response is not prompt and sustained for at least three hours, there is further deterioration in symptoms or the PEF rate, or frequent administrations of β_2-agonists are required for longer than 48 hours. The key to resolving exacerbations is to reduce inflammation. For relatively mild and transient episodes, removal of the trigger and the lapse of time may be sufficient if the acute bronchospasm is relieved by the use of β_2-agonists. For mild to moderate attacks or a gradual loss of ongoing control, a temporary or long-term increase in the doses of inhaled corticosteroids may be adequate. Many moderate to severe exacerbations are best treated initially with a short course (burst) of oral prednisone, however. The failure of symptoms and the PEF rate to further improve three to six hours after oral corticosteroids are taken indicates an inadequate response, and consideration should be given to emergency department evaluation.

Critical to the evaluation and treatment of exacerbations is preventing recurrences. It may be possible to avoid newly identified triggers, or at least to recognize the effects earlier. A review of compliance and inhaler technique is important before increasing anti-inflammatory doses. Exacerbations without a defined trigger or in which the trigger is mild or unavoidable indicate a need for an increase in (or initiation of) anti-inflammatory therapy.

Complicating Factors

Many complicating factors may make asthma difficult or impossible to control. Compliance with the patient's asthma management plan and MDI technique must be reviewed meticulously in any patient with suboptimally controlled asthma or an exacerbation. The signs and symptoms of asthma are nonspecific and may be mimicked by a variety of diseases not necessarily responsive to antiasthma medications (Table 10). A number of coexistent diseases, including gastroesophageal reflux, rhinitis and sinusitis, and allergic bronchopulmonary aspergillosis, make asthma more difficult to control. Pregnancy and surgery require planning and careful perievent management of asthma. Each patient, at evaluation and at reevaluation following an exacerbation, should have consideration given to these possibly complicating factors.

Inhaler technique greatly affects the delivery of drug to the lungs and, therefore, the efficacy of therapy. Simply asking patients to demonstrate their use of an inhaler reinforces the importance of technique to them and provides an opportunity to correct any deficiencies. Compliance is a complex interplay of patients' perceptions of the risks, benefits, and cost (time, convenience, and dollars) of therapy. Understanding a patient's perceptions of the risks, benefits, and cost can help improve compliance with the current regimen, guide modifications to improve compliance, or direct educational interventions. Of particular concern are patients whose decrement in lung function greatly exceeds their perceived symptoms.

TABLE 10.—*Disorders Mimicking Asthma*

Laryngeal dysfunction
Mechanical upper airway obstruction
Congestive heart failure ("cardiac" asthma)
Pulmonary embolism
Cigarette-related COPD with hyperreactive airways
Pulmonary infiltrates with eosinophilia
Viral bronchiolitis or *Mycoplasma* species infection

COPD = chronic obstructive pulmonary disease

Gastroesophageal reflux may trigger severe bronchospasm and increase airway hyperresponsiveness. The reflux of acidic fluid into the upper esophagus or with aspiration into the trachea is a common cause of refractory asthma. Patients with serious reflux proved by 24-hour esophageal pH probe may not have heartburn or other reflux symptoms. Neutralizing the stomach contents by administering a histamine H_2-blocker (cimetidine, ranitidine, or the like) or a proton pump inhibitor (omeprazole), with or without a prokinetic agent, removes the insult, but reductions in hyperresponsiveness and the severity of asthma may take as long as six months.

Rhinitis and particularly sinusitis may also make asthma difficult to control. Recurrent postnasal drip irritates the larynx and trachea and increases airway hyperresponsiveness. The treatment of sinusitis, rhinitis, or both may result in dramatic improvements in the control of asthma, but seldom eliminates asthma.

Allergic bronchopulmonary aspergillosis is caused by an aggressive immune response to the noninvasive growth of *Aspergillus* species in the airways. The intense local inflammatory response may result in severe asthma that requires high doses of oral corticosteroids for even marginal control. Patients typically present with episodes of fever, wheezing, productive cough, minimal hemoptysis, shortness of breath, leukocytosis, and sputum and blood eosinophilia, particularly during the winter months. Patients may expectorate brownish plugs or flecks (56%) and, occasionally, bronchial casts. The syndrome is characterized by asthma with proximal bronchiectasis, peripheral blood eosinophilia ($>1.0 \times 10^9$ per liter [1,000 per mm^3]), greatly elevated serum immunoglobulin E levels (>2,400 mg per liter [1,000 units per ml]), transient or fixed pulmonary infiltrates, immediate and intermediate skin reactivity to *Aspergillus* antigen on prick or intradermal testing, and precipitating antibodies against *Aspergillus* antigen.

Asthma in Pregnancy

The preparation for pregnancy should begin well in advance to achieve good control of a patient's asthma. In about equal proportions of patients, asthma will improve, worsen, or remain unchanged during pregnancy. The same stepped approach used for general asthma care is appropriate to care during pregnancy.[4] No therapy has been proved absolutely safe for use during pregnancy. For mild asthma treated with β_2-agonists as needed, reassuring clinical experience exists with terbutaline, albuterol,

and metaproterenol. For patients requiring anti-inflammatory therapy, the use of beclomethasone or cromolyn is supported by human studies and long experience. Bursts of oral corticosteroids are appropriate for the routine care and treatment of exacerbations because corticosteroid use is preferable to the deleterious physiologic effects of withholding treatment.

Preparing for Surgical Therapy

Achieving optimal asthma management before a surgical procedure and general anesthesia is preferable. Patients with poor asthma control or who are experiencing an exacerbation should receive a burst course of corticosteroids in an effort to optimize asthma control, if possible, before an operation. Intubation, anesthesia, and mechanical ventilation may trigger asthma exacerbations. Prophylactic intervention may avoid or reduce complications. Patients with mild asthma may require only the routine use of β_2-agonists before, during, and immediately after surgical therapy. Patients with moderate or severe asthma may benefit from a brief oral (or parenteral when the patient cannot take anything by mouth) course of corticosteroids, in addition to around-the-clock β_2-agonists. A patient's usual regimen of inhaled corticosteroids should be resumed as the oral corticosteroid therapy is tapered or discontinued. For patients treated with daily corticosteroids for more than three weeks within the past year or with the long-term use of high doses of inhaled corticosteroids (such as beclomethasone, ≥1,500 μg per day, or its equivalent), stress-dose corticosteroid therapy for possible adrenal suppression is indicated regardless of the need for the control of asthma.

Referral to Specialists

Asthma can be well managed by interested primary care physicians. Consultation with an asthma specialist, usually a pulmonologist, allergist, or immunologist, is prudent if any of the following are present:

- Doubt regarding the diagnosis of asthma.
- Complicating or contributory factors.
- Inability to control asthma or need for daily or high-dose alternate-day oral corticosteroids.
- Admission to a hospital or recurrent visits to an emergency department for asthma.

After a simple consultation or a period of stabilization, it is reasonable for patients to return to their primary care physician for continuing care. Specialist and primary care physicians should develop a plan for both ongoing therapy and the treatment of acute exacerbations, which can be carried out by the physician providing continuing care.

Looking to the Future

Further elucidation of the cellular and molecular mechanisms of asthma should lead to the development and refinement of pharmacologic interventions. A number of newer inhaled corticosteroids—fluticasone propionate, budesonide—used outside the United States show excellent promise for delivering medication with higher topical potency and lower systemic side effects. Inhibitors of arachidonate 5-lipoxygenase and antagonists of the end products of the leukotriene pathway such as leukotrienes D_4 and E_4 show promise as antiasthma agents. Cyclooxygenase inhibitors or thromboxane and prostaglandin antagonists (thromboxane A_2, PGD_2, or $PGF_{2\alpha}$) also have promise, but are less well developed. Neuropeptide receptor antagonists, platelet-activating factor inhibitors, and pharmacologic or immune modulation of T cells all have theoretical antiasthma actions that may be exploited in the future.

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Epitomes

Important Advances in Clinical Medicine

General and Family Practice

Ronald D. Cotterel, MD, and Daljeet S. Rai, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association, and the summaries were prepared under the direction of Drs Cotterel and Rai and the panel.

Screening Children for Lead Poisoning

LEAD FROM INDUSTRIAL SOURCES, home remodeling, imported ceramics, and tap water has raised serum lead levels above 480 μmol per liter (10 mg per dl) in as many as 4 million preschool children in the United States.

Although lead poisoning effects may be asymptomatic, lead toxicity causes confusion, anorexia, anemia, and neuropathies. Severe lead poisoning leads to renal tubular necrosis, lead encephalopathy, and even death. Detection and early treatment notably reduce morbidity and mortality. Serum lead levels from regional reference laboratories cost $20 to $30 and are reliable with a maximum of 7% variation. Children, especially those 6 months to 6 years old, are at the highest risk for lead poisoning. Children absorb 40% to 50% of the lead they ingest, whereas adults absorb less than 25%.

Acceptable methods of treating lead poisoning are available. For serum lead levels of 480 to 1,210 μmol per liter (10 to 25 mg per dl), treatment requires identifying the lead source and removing it from the environment. Prescribing chelating agents for patients with lead levels under 1,880 μmol per liter (39 mg per dl) is controversial. In rare cases, patients with lead levels above 1,930 μmol per liter (40 mg per dl) merit chelation therapy or dialysis. Succimer, the recently approved oral form of British antilewisite, makes the outpatient treatment of moderate lead poisoning possible. Patients should take succimer, 10 mg per kg three times a day for 5 days, followed by 10 mg per kg twice a day for 14 days. The serum lead rebound level should be monitored at day 20. The cost of 19 days of succimer therapy is $150 to $200. Succimer's rare side effects include dyspepsia in less than 5% of patients and mildly elevated aminotransferase levels in less than 10%.

Acute lead poisoning dictates a cleansing of the gastrointestinal tract. Further therapy is based on the serum lead level and the patient's clinical state. In cases of long-term lead exposure, osteoblasts incorporate lead into the bone matrix. Lead mobilization tests to remove lead from bony stores are not standard care. Using x-ray fluorescence to determine long-term lead exposure is not standard practice but holds promise for the future.

The best method for screening children, mandatory or not, is asking whether a child spends much time in a structure built before 1950 where paint is peeling or renovation is in progress or whether the child's home is located near an industrial facility using lead. Exposure history is also important if a family member has had lead poisoning or a job or hobby that involves lead or lead dust. This simple method is painless and can help determine if serum testing is indicated.

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Antioxidant Supplements and Cancer Prevention

CONSIDERABLE PATIENT INTEREST has been sparked by recent lay-press coverage of ongoing clinical trials studying the role of antioxidant supplements in the prevention of cancer and coronary artery disease. Patients frequently ask whether supplementing their diets with antioxidants is advisable. An understanding of completed and ongoing clinical research trials is helpful when addressing patient inquiries and making recommendations regarding the use of supplements.

Ample cohort and case-control epidemiologic studies have consistently yielded evidence that diets high in fruits and vegetables are associated with a low incidence of cancer. Food sources with high concentrations of antioxidant micronutrients, such as selenium, beta-carotene, vi-

tamin C, and vitamin E, seem to confer the most protection. The presumed mechanism of this protection, as elucidated by basic laboratory research and studies in animals, is the trapping of electrically unstable free radicals, thereby preventing mutagenic oxidative damage to host cell DNA.

The strong epidemiologic evidence for dietary antioxidants has prompted enough interest to initiate well-designed, large-scale, randomized, controlled clinical trials studying specific antioxidants in the form of dietary supplements. The evidence provided by these types of trials forms the basis for guidelines for use in the general population. To date, however, only two such trials have been completed, and the results have been inconsistent.

The first was a collaborative six-year study of 29,584 persons in China's Linxian County, where there is a high rate of esophagogastric cancers. In this study, significant reductions in total mortality were found in persons supplemented with beta-carotene, vitamin E, and selenium. Esophageal and gastric cancer mortality was decreased by 9% in those receiving vitamin E, beta-carotene, and selenium when compared with controls, but vitamin C had no notable effect. The study population is considered to be malnourished in these micronutrients, making the results not applicable to generally well-nourished populations such as those in the United States.

More recently, results were published of a randomized controlled trial of 29,133 Finnish male smokers who were observed for six years. The experimental groups had diets supplemented with beta-carotene or vitamin E. Not only were there no protective effects from these supplements, but those assigned to the beta-carotene group had a statistically significant rise in lung cancer risk (18%). These unexpected results raise the specter of possible detrimental effects of regular supplementation beyond the known possible risks of overdose toxicity.

If the beneficial results of the Linxian study are borne out, antioxidant supplements, if used appropriately by large populations, could substantially reduce mortality. But if the Finnish evidence is reproduced, antioxidant supplementation could actually worsen the mortality of cancer.

Fortunately, several large research trials now in progress should provide additional information when completed. These include the Carotene and Retinol Efficacy Trial (CARET) with 18,000 high-risk subjects who smoke or have histories of asbestos exposure; the French Supplementation Vitamin, Mineral, and Antioxidant study (SUVIMAX) exploring the effects of beta-carotene, vitamin E, vitamin C, selenium, and zinc on healthy adults; and the Women's Health Study, which includes 40,000 healthy US women on randomized regimens of beta-carotene, vitamin E, and low-dose aspirin. In addition, the Physicians' Health Study should be completed by the end of 1995. This 12-year trial is testing the effect of beta-carotene on cancer in 22,071 male physicians in the United States. Several of these studies will also include as end points mortality of coronary artery disease.

Health professionals may be tempted to heed the early evidence for the benefits of antioxidant supplementation by recommending that patients begin to take supplements. Unfortunately, the discrepancies in research results thus far raise the possibility of this doing more harm than good. Until more research is completed and the results analyzed, patients' interests would be better served by their health care professionals recommending with renewed effort that which we know with reasonable certainty—a healthy lifestyle includes a low-fat diet rich in fruits, vegetables, and whole grains.

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Hennekens CH: Antioxidant vitamins and cancer. Am J Med 1994; 97:2S-4S

Prostate Cancer Screening—Is the Controversy Resolved?

PROSTATE CANCER is the second leading cause of cancer death in men. Although some describe the dramatic recent increase in the incidence of prostate cancer as an epidemic, most attribute this rise to the growing use of prostate-specific antigen (PSA) as a screening test. This provides the setting for the current controversy in prostate cancer screening. A few groups suggest that routine PSA screening offers important health benefits. Most of the evidence argues against any screening for prostate cancer, however. In face of the intense media attention afforded the disease, it is important to examine the evidence carefully.

Serum PSA levels may be elevated in benign prostatic conditions such as prostatitis and benign prostatic hypertrophy and may be normal in those with prostate cancer. The American Cancer Society's National Prostate Cancer Detection Project, a study of 2,425 men aged 50 to 70 years without known prostatic disease, found that only 43% of cases of elevated PSA levels are associated with cancer. The controversy in the use of the PSA test stems from two different views of the data. The American Cancer Society, one of the proponents of the use of PSA testing, argues that the early detection of prostate cancer is associated with detecting cancer at an earlier stage, and treatment at an earlier stage is associated with improved survival. The society suggests that a positive test be followed by an ultrasonogram and biopsy of the prostate. One concern with this recommendation is that it is unable, because of a lack of data, to recommend the appropriate follow-up of those patients with an elevated PSA level whose biopsies and ultrasonograms fail to detect cancer. Because most elevated PSA levels are not associated with cancer, physicians who follow the American Cancer Society's guideline are in the uncomfortable posi-

tion of receiving no guidance on how to manage most patients who have a positive test on PSA screening.

More important, the opponents of screening note that no evidence exists that the early detection of prostate cancer improves survival. Thus, the increased detection of prostate cancer simply increases the number of people who die with known prostate cancer and does not mean that more patients are dying of prostate cancer. In fact, the death rate from prostate cancer has remained essentially constant for the past 30 years, and the category of years of potential life lost from prostate cancer ranks 21st among that for all cancers, far behind the average. In addition, the treatment of prostate cancer is associated with substantial morbidity. Recent evidence suggests that after radical prostatectomy, 90% of patients will have some degree of impotence, two thirds will have some urinary incontinence, and as many as 2% will die of the procedure. Men treated for localized prostate cancer tend to have lower quality of life than men left untreated. The PSA screening test offers almost certain harm without evidence of benefit.

Although it is clear that men at low risk should not be screened, those at high risk—men with a family history of prostate cancer and African Americans—are left in a quandary. Their increased risk decreases the frequency of false-positive PSA tests. There is still no evidence that early detection and treatment improves survival, however, and the risk of incontinence, impotence, and death persists.

Continued research in the field will provide important information that will mold future policy decisions. Until these new data are available, the wisest course is to follow the new US Preventive Services Task Force recommendation to discuss the merits and problems of PSA testing with patients who ask about it and not to offer the test routinely.

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Early Intervention for Human Immunodeficiency Virus Disease

THE INITIAL COMPONENT in the early treatment of human immunodeficiency virus (HIV) disease is the use of antiretroviral agents. Zidovudine has been the mainstay agent to prevent HIV from destroying CD4 T-lymphocyte cells. It interferes with the replication of HIV and slows the rate of CD4 cell death. Currently, oral zidovudine therapy is recommended when a patient's blood CD4 cell count drops below 500×10^6 per liter (500 per mm^3). If the CD4 cell count continues to fall to nearly half the value of when zidovudine therapy was started, then other antiretroviral agents—didanosine (DDI), dideoxycytidine (zalcitabine; DDC), and stavudine (d4T)—can be added to the therapeutic regimen. This treatment strategy may soon change, however.

Recommendations presented at the 10th International Conference on AIDS [acquired immunodeficiency syndrome] in Yokohama, Japan, call for a combination therapy approach using two or more antiretroviral agents as initial treatment of patients whose CD4 cell counts reach 500×10^6 per liter or lower. Protease inhibitors are different pharmacologic agents compared with antiretrovirals and have recently attracted much attention in preventing the progression of HIV disease. They function to block the action of the HIV protease that produces viral proteins within the cell. Investigators in the area of HIV and AIDS care are excited about the possible benefit of combining protease inhibitors with antiretroviral therapy in preventing the decline of CD4 cell counts and the progression of HIV disease.

The second component to early intervention after antiviral therapy is disease surveillance. The US Public Health Service and the American Medical Association have published similar lists of clinical symptoms, physical findings, and laboratory results that are sensitive for detecting advancing HIV disease or opportunistic infections. These clinical indicators help to identify early some of the medical problems commonly associated with HIV infection that can be treated, such as sinusitis, bronchitis, weight loss, diarrhea, thrush, anemia, granulocytopenia, cytomegaloviral retinitis, tuberculosis, toxoplasmosis, and dysplasia of the cervix. The CD4 cell count has been the most useful clinical indicator in guiding medical decisions. This marker has been used to determine the frequency of scheduled clinic visits (at most 3 months apart for patients with counts below 500×10^6 per liter) and when to begin prophylactic therapy against *Pneumocystis carinii* pneumonia and disseminated *Mycobacterium avium* complex (below 200×10^6 per liter and 100×10^6 per liter, respectively). Differences in health status have been observed among patients with similar CD4 cell counts, however. This has been attributed to differences in the amount of viral load within the lymphatic systems of patients. The polymerase chain reaction (PCR) assay quantitates the total amount of virus in the body. This assay is considered superior to CD4 cell counts in correlating clinical status, the progression of HIV disease, and the clinical response to therapy. Once PCR becomes commercially available, it is anticipated to replace the CD4 cell count as the primary laboratory measure for HIV disease.

The final component for effective early intervention is disease prevention. The Centers for Disease Control and Prevention has recently published guidelines for vaccinating persons with HIV infection against pneumonia, influenza, hepatitis, and *Haemophilus influenzae*.

Investigators also propose new strategies in early intervention regarding mental health wellness, proper nutrition, dental hygiene, fitness exercise, stress reduction, safe sex, substance abuse abstinence, and smoking cessation. The aims of these recommendations and strategies are to equip primary care physicians with the knowledge and information to responsibly manage the health care of HIV-infected patients.

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Angiotensin-Converting Enzyme Inhibitors in Congestive Heart Failure

ANGIOTENSIN-CONVERTING ENZYME (ACE) inhibitors, a remarkable class of drugs developed from the initial discovery of molecules with ACE-inhibiting properties in the venom of Brazilian pit vipers, have been available for commercial use in the United States for more than a decade. First used for treating hypertension, it soon became appreciated that ACE inhibitors were also highly effective in the treatment of heart failure. In fact, much data exist to show that ACE inhibitors significantly reduce mortality in patients with moderate and severe heart failure, improve functional capacity, and prevent hospital admissions. Moreover, ACE inhibitors have been shown to decrease the development of symptomatic heart failure in patients with asymptomatic (New York Heart Association class I) disease. Despite these well-documented benefits, fewer than 50% of patients with heart failure are currently treated with ACE inhibitors.

Surveys of clinicians providing care to patients with heart failure suggest that physicians are reluctant to use ACE inhibitors in these patients because of the fear of causing hypotension. For this reason, ACE inhibitors are often reserved only for those patients with heart failure and concomitant hypertension. In the studies of the treatment of heart failure with ACE inhibitors, however, notable hypotension was distinctly unusual. Because of the profound clinical and economic benefits of ACE inhibitor therapy in these cases, virtually all patients with heart failure should be treated, and they should be treated with moderate doses, such as captopril, 50 mg three times a day, if tolerated. Patients in whom the use of ACE inhibitors is contraindicated include those with a history of allergy or a severe reaction to ACE inhibitors, those with refractory hyperkalemia (potassium level > 5.5 mmol per liter), and those with symptomatic hypotension. Patients with renal insufficiency (creatinine level > 265 μmol per liter [>3.0 mg per dl]) and those with systolic blood pressures less than 90 mm of mercury may be treated with ACE inhibitors, but they have a higher rate of complications and must be monitored carefully, often with a consulting cardiologist.

Angiotensin-converting enzyme inhibitors are thought to have a "class action" in patients with heart failure; therefore, no single agent is preferred over another. In patients considered to be at high risk for complications from ACE inhibitor therapy, institute treatment with a small dose of a short-acting drug (such as captopril, 6.25 mg) and observe the patient carefully for several hours. Patients taking diuretics should be examined for evidence of hypovolemia, and fluid and electrolyte disorders, if present, should be corrected before beginning ACE-inhibitor therapy. Patients should be seen in two days and at one week, and renal function, serum potassium levels, and blood pressures should be observed carefully. The ACE-inhibitor dosage should be increased slowly at two- to three-week intervals.

Angiotensin-converting enzyme inhibitors in the treatment of heart failure should be thought of not only as antihypertensive agents. Current evidence shows that they have a powerful effect on the myocardium at the cellular level and possibly retard the development of left ventricular hypertrophy. The vast majority of patients with heart failure are candidates for treatment with ACE inhibitors. Moreover, all patients suffering a myocardial infarction—except those in whom it is the first infarction and the infarction is inferior wall, small, nontransmural, and uncomplicated—should have their ejection fraction determined by echocardiogram or radionuclide ventriculogram. All those with ejection fractions below 40% should be treated with ACE inhibitors, even in the absence of symptoms or signs of heart failure.

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Cryptorchidism

CRYPTORCHIDISM, from the Greek "hidden testes," is the most common urologic problem of neonates and young children. The estimated prevalence of cryptorchidism is about 3% among full-term neonates; among premature infants and those with low birth weights, it has been reported to be as high as 30%. The problem affects the right testis more frequently.

The consequences of a permanently undescended testis are potentially deleterious. Besides diminished fertility and psychological trauma, an undescended testis is the major risk factor for testicular cancer. Persons with

undescended testes have a 22 times higher risk for testicular cancer than those with normal testes, and the risk for cancer in the contralateral descended testicle is also higher than in normal testes. Seminoma, the most common tumor, usually manifests during the second or third decade of life.

Careful examination of an infant's genitalia is essential. If a testis is not palpable in the scrotum, the inguinal canal should be investigated by palpating it from the internal to the external ring. The position of a palpable testicle within the canal must be noted and an attempt made to "milk" it down toward the scrotum. If the testicle can be brought into the scrotum manually, then it represents a retractile testis, most of which are at the suprascrotal area. Another helpful maneuver to bring the testis down is to examine the infant with the ipsilateral leg crossed, which relaxes the cremasteric muscle and allows the testicle to descend into the scrotum.

If no testicle is palpable, the challenge is to locate it. Several studies are available for this purpose—gonadotropin stimulation, venography of the spermatic vessels, thallium imaging, abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Abdominal ultrasonography is most sensitive when the testis is next to or along the inguinal canal and is less sensitive in locating a testis that is in the abdomen. Even though CT and MRI are both sensitive techniques, MRI exposes the infant to no radiation and appears to be superior at evaluating cord structure. Venography of the gonadal vessels is useful but is technically difficult, invasive, and involves radiation exposure. Laparoscopy is the definitive method of locating an undescended testis; it provides direct visualization of the anatomy and information for planning surgical treatment.

In most cases, the natural history of an undescended testis is spontaneous descent, usually occurring within the first year of life and, in most cases, within the first three months of life. If no descent is observed by about 1 year of age, urologic consultation is indicated.

Therapy with human chorionic gonadotropin (hCG) hormone has been effective. The success rate is better for bilateral than unilateral undescended testes: as high as 40% and 30%, respectively. Treatment regimens vary but usually involve administering hCG every other day or twice a week for two to five weeks.

Orchiopexy is strongly advised for impalpable testes when hormonal therapy fails or when a mechanical or anatomic cause of cryptorchidism is suspected. Early surgical treatment is advocated in view of the possible beneficial effect on fertility and the possible decreased risk of cancer. Several surgical techniques are used. All involve isolating and ligating the hernial sac, freely mobilizing the cord with its vascular and vasal components, and fixating in the scrotum.

The clinical evaluation of neonates with an undescended testis must always include frequent discussions with the parents—taking time to answer their questions, providing objective information, presenting and explaining alternative therapies, and reducing parental anxiety whenever possible. Primary care physicians have an important role in the care of children with cryptorchidism.

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Neonatal Group B Streptococcus Infection—Recommendations for Screening and Prophylaxis

GROUP B STREPTOCOCCUS is the most common infectious cause of neonatal morbidity and mortality in the United States, causing disease in 12,000 to 15,000 newborns each year. The maternal cost is extremely high as well, with 50,000 cases of maternal infections yearly.

Of the 15% to 40% of women who are carriers of group B streptococcus and colonized in the gastrointestinal tract and vagina, 50% give birth to infants colonized with this organism, with 1% to 2% of these neonates clinically infected. The mortality for neonates with early-onset (the first week of life) group B streptococcus infection is 15% or higher. Risk factors identified by the American Academy of Pediatrics (AAP) or the American College of Obstetricians and Gynecologists (ACOG) that increase the infection or attack rate in neonates are prematurity (labor before 37 weeks), premature rupture of membranes, maternal fever, prolonged rupture of membranes (>18 hours), a previously infected child (ACOG only), and multiple births (AAP only).

A second syndrome, late-onset group B streptococcus infection, is seen in 0.5 to 1 per 1,000 live births. The patient usually is diagnosed with sepsis or meningitis, which may be due to either a maternal or community (nosocomial) infection.

To lower the rate of early-onset neonatal group B streptococcal infection from the current rate of 3 per 1,000 live births, multiple screening and treatment protocols have been recommended. Formulating screening and treatment policies is difficult because of a number of factors. Identifying and treating women at a high risk would prevent only a portion of the neonatal infections. The colonization of women by group B streptococcus is a transient phenomenon; a woman with a positive culture at 28 weeks may be culture-negative at term, and vice versa. In addition, obstetrics and neonatology are such emotionally and liability-charged areas, with perfect outcomes now expected and demanded, that even the Trial Lawyers of America have developed their own "guidelines."

Because of these factors, a consensus on screening and treatment guidelines has yet to be reached. At present, an AAP policy statement (RE9261) recommends chemoprophylaxis for those maternal carriers who have identified risk factors. In contrast, ACOG argues against universal screening, but does recommend intrapartum antibiotic chemoprophylaxis for all patients with identified

risk factors, regardless of culture results. When consideration is given to the difficulties in obtaining universal cultures; the inability of early culture results to predict intrapartum maternal colonization; the unavailability of an accurate, reliable, and rapid detection method; and the understanding that the universal eradication of group B streptococcus disease is not currently possible, the ACOG recommendation of intrapartum treatment based solely on risk factors seems to be a realistic, practical, and cost-effective means of decreasing the incidence of group B streptococcus disease. For those interested in following this issue, a Centers for Disease Control and Prevention consensus statement is expected later in 1995.

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Advances in Immunization

IMMUNIZATION SCHEDULES are changing so rapidly that many official record cards are out of date by the time they are distributed. Fortunately, the changes have simplified immunization schedules while actually decreasing the number of injections through the use of combined vaccines.

The long-awaited varicella vaccine has just arrived, and recently the timing changed for the live oral poliovirus vaccine (OPV) and the measles-mumps-rubella (MMR) vaccine. Other advances are the recommendations for universal immunization against the hepatitis B virus, the acellular pertussis vaccine (aP), and the second MMR.

The varicella vaccine to prevent chickenpox was released in May 1995, and the American Academy of Family Physicians and the American Academy of Pediatrics already recommend it for general use. Administer one dose between age 12 months and 12 years or two doses eight weeks apart for patients 13 years or older who have not already had varicella infection. As a live vaccine, it has the potential for long-lasting and has demonstrated only minimal risk of person-to-person transmission.

The Advisory Committee on Immunization Practices of the United States Public Health Service now recommends that the third dose of OPV, previously removed from the 6-month schedule, be resumed and that the 18-month dose be deleted. The earlier dose is equally efficacious and may help ensure adequate immunization at a time when parents are most attentive about physician visits and the child is simultaneously receiving other immunizations. The final preschool dose at 4 to 6 years of age remains to round out a four-dose series at 2, 4, and 6 months and 4 to 6 years of age.

The first and only dose of MMR was traditionally given at age 15 months. Physicians have always had the option to administer the MMR as early as 6 months of age when outbreaks occur. If given at 12 months of age or older, it was not necessary to repeat the dose at 15 months. The logical progression of this thinking has resulted in the current recommendation to immunize the general population starting at 12 months. After multiple measles outbreaks occurred at college campuses in the 1980s, the booster dose of MMR was advised at 4 to 6 years or 11 to 12 years of age. The preschool timing seems preferable because so few middle-school–aged students return for routine well-child care compared with the mandatory preschool physical examination.

The incidence of the vertical transmission of hepatitis B virus can be decreased by screening women during their pregnancy. Babies born to carriers of the virus should receive hepatitis B immune globulin, and the hepatitis B virus vaccination should be started as soon as possible after birth. All other infants should be immunized or immunization arranged for before they are discharged from the hospital. The second dose should be given at least one month later, typically at the two-month well-child visit or at the vaccination clinic. The third dose is due at six months. Booster doses are not yet recommended, but because of waning levels of immunity, they may be indicated every ten years, similar to tetanus toxoid boosters. We hope that a combined hepatitis B virus and tetanus toxoid booster will surface if this is the case.

Concern regarding reactions to the pertussis component of the diphtheria and tetanus toxoids and pertussis (DTP) vaccine has spawned the development of the acellular pertussis (aP) vaccine. The aP vaccine decreases the incidence of local reactions, fever, and irritability, but rare occurrences of temporally related neurologic events have been reported. Unfortunately, it has not yet been approved for use before the 15-month dose. It is available, combined with diphtheria and tetanus toxoids, as the DTaP. Soon it may be approved to be combined with the *Haemophilus influenzae* type b (HIB) vaccine to reduce the number of injections at the 15-month visit, the same way that combining the DTP and HIB has shaved off a separate injection at 2, 4, and 6 months of age.

Risks and benefits of immunizations need to be considered on an individual basis. Patients who are immunocompromised or who have family members who are immunocompromised, patients with allergies to eggs, and those with underlying neurologic disorders require special care. A suboptimal vaccine is available for tuberculosis, but if multiple drug-resistant tuberculosis outbreaks continue, it or an improved vaccine may see widespread use.

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Hepatitis B Immunization for Adolescents

In 1991 and 1992, the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, and the American Academy of Family Physicians presented new guidelines for the prevention of hepatitis B. These guidelines propose a broad-based immunization program that includes all newborns and others at high risk, including adolescents. The initial announcement was met with a flurry of controversy as parents and providers balked at adding three more immunizations to an already-crowded newborn immunization schedule.

This hesitancy was not based on a lack of respect for the disease. Hepatitis B causes substantial morbidity and mortality in this country. Each year 300,000 new cases are reported, with about 5% of these patients becoming a long-term carrier, increasing the risk of transmissibility and the development of hepatocellular carcinoma. The chances of the chronic carrier state developing is highest when the infection occurs in the newborn period; as many as 90% of infected newborns become carriers. Still, the disease is rare in childhood, and only about 1% of the reported cases occurs in children younger than 10 years.

A concern about the recommendations involves the lack of emphasis on adolescent immunization. Although the initial 22-page CDC recommendation included a statement on adolescents, all of the educational material and most of the press coverage focused on newborns. Adolescents are an important group, however, with about 25% of hepatitis B reported each year occurring between the ages of 10 and 20 years and about 5% of these teens becoming carriers. For these reasons, more teens than newborns become carriers each year, even though newborns have a higher conversion rate. Adolescents are important not only because of these health problems but also because they engage in more behaviors that transmit the disease. Any program that focuses on preventing disease in adolescents thus immediately decreases the risk of transmission.

Serious problems with adolescent immunization are cost and compliance. Adolescents require a full dose of the vaccine, which increases costs. In addition, the vaccine requires three separate immunizations. This increases costs (presumably a physician visit accompanies most of these immunizations) and decreases compliance (newborns receive other immunizations at the same time so additional trips are not needed).

Recent advances address the two problems with adolescent immunization programs. First, a growing number of insurance companies now cover the immunization for any patient younger than 20 years. This lowers the cost barrier. In addition, the CDC is conducting demonstration projects to determine the feasibility of a school-based immunization program. This would not only decrease the total costs of administering the vaccine, but would increase compliance because three visits to a physician would not be necessary.

Hepatitis B remains a serious health concern. Although the immunization of newborns helps to decrease the risk in the first decade of life, such a program has a minimal effect on the immediate problem because so few young children get the disease. The recent move to develop cost-effective methods for immunizing large numbers of adolescents will go far in ensuring that this high-risk group is protected. Until these programs are implemented, physicians caring for adolescents should offer this group the immunization along with advice regarding sexual abstinence or safer sex practices and the avoidance of illicit drugs.

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Breast Cancer in Pregnancy—A Diagnostic and Therapeutic Challenge

Pregnancy-associated breast cancer, as defined by carcinoma of the breast diagnosed during pregnancy or within the first postpartum year, is the second most common malignant neoplasm in pregnancy after cervical cancer. Because women are delaying childbearing and breast cancer is occurring at an earlier age, the incidence is expected to increase. Of breast cancer patients younger than 30 years, 25% have been pregnant within the past year. The incidence of pregnancy-associated breast cancer is between 1 in 3,000 and 1 in 10,000 pregnancies.

Although these women have extensive contact with health care professionals, the diagnosis is usually delayed. Only a small percentage of patients are diagnosed and treated during pregnancy. The majority (80%) of patients are diagnosed within 12 weeks of delivery, but 50% of these patients had a mass noted during the pregnancy. The mean size of the tumor is 3.5 cm.

Unfortunately, making the diagnosis during pregnancy is fraught with difficulties. Normal changes associated with pregnancy, including the enlargement of the lobules, increases in the stroma, and hyperemia, serve to obscure the mass during pregnancy and breast-feeding. Ultrasonography should be used to identify cysts and galactoceles and to locate a discrete mass. Mammography, a mainstay of breast cancer surveillance, is of little assistance during pregnancy and lactation because of normal changes in the breast.

Biopsy should be considered the mainstay of diagnosis. In pregnant patients, open biopsy under local anesthesia should be done whenever possible. A fetal death rate of 1 per 134 was reported for breast biopsy done under general anesthesia. In lactating patients, biopsy has a high complication rate. Lactation should be stopped before an

open biopsy. The use of bromocriptine or binding with ice packs should be considered. Risks include infection, which can be reduced by the use of antibiotics (which are excreted into the breast milk), and milk fistulas, which occur more frequently with lesions that are centrally located. A fine-needle aspirate may be extremely difficult to assess because of the cytologic changes that occur with lactation.

During pregnancy, staging may be difficult. Chest radiographs may be obtained, as may a computed tomographic scan of the head if there are suggestive neurologic findings. Computed tomography of the abdomen is contraindicated in the first or second trimester, and bone scans are contraindicated throughout pregnancy.

Whereas breast preservation is generally always considered when discussing treatment options with a woman with breast cancer, modified radical mastectomy is the only surgical option available during pregnancy. Breast preservation is not an option during pregnancy due to morbidity associated with other treatment plans. Radiation therapy is not an option due to the scatter that occurs from the mother's bones and organs to the fetus. Chemotherapy, which generally crosses the fetal-placental barrier and affects rapidly dividing cells, may lead to a fetal malformation (12.7% risk) and is contraindicated during the first 15 weeks of pregnancy. Chemotherapy may be used after 15 weeks of gestation, but may lead to a low birth weight (40% risk) and possible developmental delay. Teratogenicity, such as lymphoma and leukemia, has been reported.

The termination of pregnancy historically has been encouraged to improve outcome, but recent series fail to show any additional benefit. The need for chemotherapy or radiation therapy may lead to a consideration of termination.

Breast cancer found during pregnancy has had a poor prognosis. Studies demonstrate that the stage for survival rates is the same for pregnant and nonpregnant patients. Unfortunately, breast cancer found during pregnancy is often in an advanced stage. The presence or absence of affected nodes is an important prognostic factor. Five-year survival rates have been found to be 82% for patients with normal nodes compared with 47% for patients with cancerous nodes. Because of the aggressive nature of breast cancer during pregnancy, modified radical mastectomy for potentially curable disease should not be delayed, especially in the third trimester.

Physicians and nurse midwives must do routine breast examinations during early prenatal care. Pregnancy is generally a joyous time for a woman and her family, but the diagnosis of breast cancer irrevocably alters a woman's life. Especially during pregnancy, the use of social support systems is critical to assure appropriate care of the newborn and to increase the likelihood that the family will survive the health crisis.

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Alerts, Notices, and Case Reports

Mycotic False Aneurysm of the Superficial Femoral Artery

Delayed Complication of Salmonella Gastroenteritis in a Patient With the Acquired Immunodeficiency Syndrome

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MYCOTIC INFECTION of a blood vessel arises from the bacterial seeding of an atherosclerotic plaque or other damaging processes such as blunt trauma that may predispose to the development of a pseudoaneurysm (false aneurysm). Gram-negative bacilli, chiefly *Salmonella* species, account for roughly 35% of such cases.[1] *Salmonella enteritidis* is the serotype responsible in 40% of the latter cases of infection, a proportion similar to its overall isolation rate for gastrointestinal disease in the United States.[2,3] *Salmonella* species have long been recognized as a common cause of mycotic aneurysms in persons without human immunodeficiency virus (HIV) infection.[4] Risk factors for this vascular complication include advanced age,[5] the intra-arterial administration of illicit drugs,[6,7] and ongoing septicemia from salmonella infection.[8] Of patients older than 50 years not infected with HIV but with salmonella bacteremia, it is estimated that an intravascular focus of infection develops in 25%.[9]

The literature on the acquired immunodeficiency syndrome (AIDS) is sparse regarding descriptions of mycotic aneurysm infection due to *Salmonella* species, with cases limited to involvement of the abdominal aorta.[10-13] *Salmonella enteritidis* is an important cause of diarrhea in HIV-infected persons[14]; thus, it is surprising that mycotic aneurysms are not more commonly described in patients with AIDS. Indeed, recurrent salmonella bacteremia serves as an AIDS-defining illness.[15,16]

Although no angiographic study exists that looks at the presence of peripheral vascular disease in AIDS patients, the infrequent reporting of cases of mycotic aneurysms in such persons is postulated to be due to the epidemiology of HIV infection, which involves younger persons less apt to have underlying atherosclerotic disease. In addition, mycotic aneurysms often cause vague symptoms.[6,11] Finally, physician suspicion for this complication is probably low.

Herein is described a unique case of an AIDS patient in whom a superficial femoral artery pseudoaneurysm due to *S enteritidis* developed as a delayed complication of infectious diarrhea. The clinical circumstances, symptoms, and physical signs that should alert physicians to the presence of a mycotic aneurysm are highlighted. Recommendations regarding diagnostic testing are provided for the detection of this treatable but possibly life-threatening illness.

Report of a Case

The patient, a 39-year-old homosexual man, first sought medical care at the Washoe County District Department of Health's Early HIV Intervention Clinic (Reno, Nevada) in March 1992. On presentation, he showed advanced disease manifested by cachexia and a $CD4^+$ lymphocyte count of 13×10^6 per liter (13 cells per mm^3). His baseline physical examination was remarkable only for severe exfoliative dermatitis of his hands and feet. There was no history of AIDS-related opportunistic infections. The patient had a 30-pack-year smoking history. A regimen of zidovudine and dapsone was prescribed. Severe dermatologic manifestations dominated the patient's course, requiring the use of potent topical steroids. He did remarkably well with only occasional attacks of thrush. In March 1993, zidovudine was discontinued, and a regimen of didanosine was prescribed. In June 1993, he had an abrupt attack of bloody diarrhea. The patient did not seek medical advice and took loperamide hydrochloride (Imodium) for three days. This last medication was stopped by the clinic physician, who prescribed a ten-day course of oral ciprofloxacin, 500 mg twice a day. The patient responded quickly to this medication, but discontinued ciprofloxacin after only two days. Culture of a stool specimen isolated a group D *Salmonella* serotype (*enteritidis*). Ova and parasite analysis was negative. The patient did well without a recurrence of his diarrhea.

In mid-December, the patient fell on an icy sidewalk, noting right thigh pain and swelling. Noninvasive studies of his lower extremities were obtained to rule out a traumatic deep venous thrombosis. Duplex imaging showed an aneurysm of the right superficial femoral artery. On admission, the patient was not acutely ill, and his temperature was not elevated. On physical examination, he had psoriasis, thrush, and a tender mass located along the adductor canal just above the right knee. Distal pulses of the right leg were intact, and no pulsatile mass was noted. Admission laboratory studies revealed an established low-grade anemia, a normal leukocyte count, an increased Westergen sedimentation rate of 85 mm per hour, and normal coagulation values. Arteriography

(Zell SC: Mycotic false aneurysm of the superficial femoral artery—Delayed complication of salmonella gastroenteritis in a patient with the acquired immunodeficiency syndrome. West J Med 1995; 163:72-74)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

demonstrated atherosclerotic plaquing of the distal infrarenal aorta and focal 80% stenosis at the origin of the right common iliac artery, requiring dilatation by balloon angioplasty. Subsequently, a large, 5-cm pseudoaneurysm arising from the distal superficial femoral artery was seen. Blood specimens were drawn for culture and the patient's pain controlled with analgesics. Surgical dissection the next morning isolated this pseudoaneurysm. An incision resulted in the drainage of pus, and Gram's stain of this material showed numerous gram-negative rods. The involved vessel was completely disrupted and removed with an end-to-end anastomosis (4 cm in length) completed using an autogenous saphenous vein graft. The area was debrided, resulting in vascular reconstruction through an uninfected tissue plane.

Postoperative intravenous antibiotic therapy was begun empirically using metronidazole, gentamicin sulfate, and vancomycin hydrochloride. The following day, cultures of both the blood and a specimen from the infected pseudoaneurysm isolated *Salmonella* group D (*enteritidis*). The organism was susceptible to a wide variety of antimicrobial agents, and intravenous cefazolin was chosen. The patient did well postoperatively without any fevers or evidence of distal embolization. An echocardiogram revealed no valvular vegetations to suggest bacterial endocarditis. He felt well enough to be discharged two weeks after the operation and completed an oral course of ciprofloxacin, 750 mg twice a day, over a four-week period.

Discussion

This case describes the development of a pseudoaneurysm of a superficial femoral artery as a delayed complication from infectious diarrhea due to *S enteritidis*. No doubt the patient's lack of compliance in completing a full course of antibiotic therapy contributed to this unusual vascular problem. This patient had unusually severe, preexisting, atherosclerotic large-vessel disease. Indeed, he had an 80% stenosis of the right common internal iliac artery requiring balloon angioplasty to visualize his distal extremity vasculature. Although he had rapid resolution of his diarrheal symptoms, bacteremia from *S enteritidis* likely ensued and established a vascular focus of infection. Another contributing factor may relate to the patient's self-medication with an antimotility drug early in the course of his diarrheal illness. This may have prolonged the intestinal clearing of salmonella infection, increasing his chance of a sustained period of bacteremia. In healthy non–HIV-infected persons admitted to hospital for disseminated salmonellosis, a common historical finding is the oral administration of an antidiarrheal agent.[17]

This case highlights the difficulty in diagnosing a mycotic aneurysm infection in a patient with AIDS. This complication is not a common opportunistic infection. A recent Multicenter AIDS Cohort study listing the AIDS-defining conditions in 844 persons did not report vascular complications from salmonella bacteremia in the list of illnesses.[18] In earlier case reports of mycotic aneurysm due to this organism in HIV-infected persons, the abdominal aorta was involved.[10,12,13] In such cases, prodromal symptoms have been vague abdominal discomfort and low-grade fever.[11] Physicians must maintain a heightened awareness of this vascular complication, especially when caring for patients with AIDS who are older or have a heavy smoking history and who show physical evidence of atherosclerotic disease. Following a diarrheal illness due to *S enteritidis* infection in such patients, the presence of unexplained abdominal pain or fever should prompt a thorough vascular examination. Distal extremity pulses must be assessed for their symmetry and the presence of a pulsatile mass evaluated.[19]

The diagnosis in this patient became evident from the striking physical abnormalities of swelling in the groin characteristic of femoral artery aneurysms.[20] Although such aneurysms have been well described in patients with injection drug use,[7] clinically differentiating them from a groin abscess is difficult, and diagnostic attempts at incision and drainage may result in brisk bleeding.[6] Noninvasive ultrasound studies may serve for initial screening purposes due to their lower cost, availability, and ease of accurately determining the size and location of an aneurysm.[19] Abnormal results must be followed by angiographic evaluation, however.[21] The latter provides detail of the pseudoaneurysm and the integrity of distal runoff and helps to assess limb viability.

Although surgical experience with the treatment of mycotic aneurysms due to *S enteritidis* infection is limited, reports of cases in HIV-infected patients describe success, with long-term survival and graft patency of as long as 21 months.[11] Surgical success is related to the isolation and resection of the pseudoaneurysm, the debridement of locally infected tissue, and vascular reconstruction through uninfected tissue planes using autogenous grafting.[22,23]

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Prevention and Management of Hypernatremic Dehydration in Breast-fed Infants

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SEVERAL REPORTS in the medical literature over the past 15 years have detailed the clinical course of critically ill breast-fed children with hypernatremic dehydration shortly after birth, all of whom required vigorous therapeutic efforts.[1-7] The child in the case reported here is such an infant, who became desperately ill with hypernatremic dehydration. Like some but not all of those in the cases reported, he seems to have recovered without sequelae.

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Report of a Case

The patient was born to a 23-year-old gravida 1, para 0 woman at 41 weeks' gestation, weighing 2,843 grams after an uncomplicated pregnancy. Apgar scores were 8 at one minute and 9 at five minutes. The nursery stay was without complication, and the nurses' notes indicated that the mother was breast-feeding well. A circumcision was done when the infant was about 30 hours old, and mother and infant were discharged several hours later. Weight on the morning of discharge was 2,727 grams (decreased 4.8% from birth). As was usual for babies discharged within 48 hours, the child had an appointment scheduled three days later. At that visit, the mother expressed concern over the infant's fussiness during nursing and infrequent stools and urination. The findings of an examination were normal except for mild icterus (the serum bilirubin level was 227 μmol per liter [13.3 mg per dl]). The infant at this time weighed 2,560 grams (10% less than at birth). The mother strongly desired to breast-feed her infant and was given recommendations on infant care and feeding.

At 7 days of age, the patient was brought to the clinic by his parents who were concerned because he had had fever for about 8 hours and no urine output for approximately 24 hours. He was febrile, moderately lethargic, and markedly dehydrated, with dry mouth, dry sunken eyes, and a pronounced loss of skin turgor. He weighed 2,132 grams (24% below birth weight). The baby was moderately jaundiced.

Initial laboratory results included the following: serum sodium 182, potassium 3.5, chloride 138, and bicarbonate 25 mmol per liter; urea nitrogen (BUN), 73.2 mmol per liter (205 mg per dl); and creatinine, 212 μmol per liter (2.4 mg per dl). The leukocyte count was 9.0×10^9 per liter (9,000 per mm^3) with a normal differential; hemoglobin, 137 grams per liter (13.7 mg per dl); and platelet count, 321×10^9 per liter (321,000 per mm^3). A blood culture was later reported as negative for pathogens, as was the culture of the spinal fluid; the cerebrospinal fluid was xanthochromic (probably due to neonatal jaundice; the serum bilirubin level was 258 μmol per liter [15.1 mg per dl]), with 45 erythrocytes $\times 10^6$ per liter and 1 monocyte $\times 10^6$ per liter; the glucose level was 2.7 mmol per liter (48 mg per dl), and the protein level was 0.77 grams per liter (77 mg per dl).

An intravenous catheter was placed, and the child was given two boluses of 20 ml per kg of a solution of normal saline with 5% dextrose over the first hour. Antibiotics (ampicillin and gentamicin sulfate) were administered intravenously (they were discontinued two days later when the cultures were reported as negative). When the serum sodium level became available, the intravenous fluid was changed, first to dextrose with 0.675% sodium chloride and then to dextrose with 0.45% sodium chloride when no seizures occurred. The fluid infused was calculated to replace losses slowly over 24 hours to avoid rapid fluid shifts. Urine output

remained low during the first two days, but the child was intermittently active and alert. The serum sodium level fell slowly at first, presumably because of the relatively high sodium concentration of the infused fluid and the sodium accompanying the ampicillin. The serum sodium level fell to 178 mmol per liter 19 hours after admission, 171 mmol per liter on the second hospital day, 165 mmol per liter on the third, 158 mmol per liter on the fourth, and 154 mmol per liter on the fifth hospital day. Renal function study values fell more rapidly, with the BUN reaching 4.6 mmol per liter (13 mg per dl) and the creatinine 88.4 μmol per liter (1.0 mg per dl) on the third hospital day. The fractional excretion of sodium on the second hospital day was 0.8, well within the range for prerenal azotemia. The urine osmolality on the second day was 472 mmol per kg (472 mOsm per kg), appearing to rule out diabetes insipidus. Specimens of the mother's breast milk were obtained about 36 hours after she had last breast-fed her infant; milk from the left breast had a measured sodium level of 78 mmol per liter, and from the right breast the value was 58 mmol per liter. Normal values for colostrum have been reported to be 22 ± 12 mmol per liter; for mature milk at two to three weeks, it is 7 ± 1 mmol per liter.[8] The patient's mother appeared healthy and well hydrated and had no signs of malnutrition or cystic fibrosis, conditions that could elevate sodium levels. Her serum sodium level was not measured.

The infant's urine output increased by the end of the second hospital day, reaching 6 ml per kg per hour by the morning of the third day. After the breast milk sodium level became available, the mother decided not to breast-feed further. The medical staff, uncertain as to the likelihood of the problem recurring, did not attempt to convince her otherwise. Formula feeding was begun on the third hospital day, with the infant showing excellent weight gain before discharge.

The patient was discharged on the sixth hospital day with normal results on an examination and taking formula well. He has been seen for routine follow-up since, appearing to develop and grow normally. When last seen at 3 years of age, his height and weight were at the 35th and 50th percentiles, respectively. The patient's mother had decided against breast-feeding her second child, despite our assurance that a similar occurrence would be unlikely.

Discussion

Several issues arose in a sequential fashion in the treatment of this patient, starting with the urgent need to treat shock:

- How should immediate resuscitation be accomplished?
- What was the cause of the severe hypernatremia?
- What problems occurred in this breast-feeding dyad that led to the severe dehydration?
- What is the prognosis for this infant and others like him?
- Should the woman have resumed breast-feeding once her infant had been treated?
- What education should women new to breast-feeding receive before and after delivery?
- What fail-safe mechanisms should be in place to avoid possible disasters such as this?

It was clear on admission of this child that fluid resuscitation was urgent. Human plasma protein fraction (Plasmanate) or albumin might have been chosen; a normal saline solution is most readily available in such an emergency. We were fortunate to be able to establish an intravenous cannula almost immediately; otherwise, an intraosseous needle might have been placed. Because the presentation of a child in shock is not unlike that of septicemia, a workup for septicemia and initial treatment with antibiotics are often warranted.

When the infant's high serum sodium level was reported, the diagnosis of the cause of that condition became a priority, along with the careful observation of the infant and his serum sodium level to avoid the seizures that can occur from too rapid lowering of the sodium level.[4] Several causes of hypernatremic dehydration have been listed[9]: some, such as cerebral injury, prolonged fever, salicylate toxicity, and hyperventilation, seemed unlikely with the history and the examination results. Diabetes insipidus was ruled out by the infant's ability to concentrate the urine to the degree expected for a newborn. Excessive salt intake remained the most likely possibility. Although cases of child abuse by salt poisoning have been reported, this seemed exceedingly unlikely with this family. Because there was no fluid intake other than breast milk, we measured the breast milk sodium concentration as the most likely source of a high sodium intake. The breast milk sodium level at 8 to 14 days averages 13.1 ± 0.6 (standard error of the mean) mmol per liter.[8] The mother's breast milk sodium level at eight days measured 58 and 78 mmol per liter in the right and left breast, respectively. These measurements appeared to have established the cause of the hypernatremia; a fall in the sodium level has been documented each day after birth, making it likely that the level in this mother's milk was even higher on earlier days.[8] One author studied 130 women who started breast-feeding, measuring breast milk sodium levels from day 3 to day 12.[10] Women who failed at breast-feeding did not have the same drop in breast milk sodium values seen in women who succeeded. Thus, in the case reported here, the mother's high breast milk sodium values may have indicated that she would not have succeeded at breast-feeding.

How did the severe dehydration develop? We do not have a clear answer to this question. Motivation was not a problem: events before, during, and long after the crisis have convinced us that the patient's mother cared deeply for him and was strongly motivated to breast-feed him successfully. By history, she was feeding him frequently enough (every 2 to 3 hours). She apparently was eating and drinking sufficiently. How well did the family know the signs of dehydration and severe illness?

Apparently not well enough. Should we have recognized the impending problem at the first clinic visit at 3 days of age? According to some authors, a 10% weight loss is well within 2 standard deviations of the mean maximal weight loss (5.8% ± 3.2%) for a breast-feeding infant.[11]

The prognosis for infants with severe dehydration has generally been good, but not invariably so. A case has been reported of an infant with a serum sodium level of 189 mmol per liter who had a normal Bayley Infant Mental and Motor Development Index at age 11 months.[6] Other authors, in reporting on four breast-fed infants with severe dehydration (3 of whom had serum sodium levels ranging from 173 to 190 mmol per liter), found all to have normal development at 2 years, though one had nystagmus.[5] On the other hand, the course of an infant was described who presented with severe dehydration and a serum sodium level of 176 mmol per liter; that child has had persistent seizures and severe developmental delay, although the child's premorbid condition was not known.[7] A good neurologic outcome has been reported in another infant, although elevated blood pressures persisted in that patient through the period of follow-up.[3] Our patient appears to have done well.

One of the most difficult questions in this case is whether the mother should resume breast-feeding. The issue of being able to breast-feed once a high sodium level has been detected in the milk has not been addressed.[10] Will the milk continue to be high in sodium, placing the infant again at a high risk of hypernatremia? In the case of hypernatremic dehydration in a breast-fed infant,[7] maternal milk sodium levels were twice normal (16 mmol per liter) at 30 days; the author recommended against allowing the child to return to the breast. Another author, however, noted a rapid fall in breast milk sodium to normal values by about 21 days, and stated the following[6(p372)]:

> Because the primary cause of the disorder [hypernatremic dehydration] is probably insufficient lactation and not elevated sodium in the breast milk, therapy should include supporting the mother and giving her the opportunity to successfully relactate. . . . Relactation can be accomplished physiologically through frequent breast pumping and supplementation using a nursing supplementer while the infant provides sucking stimulation to the breasts.

Unfortunately, in this situation, we were uncertain of the danger to the infant if the mother resumed breast-feeding; by the time we found Thullen's paper, the mother, sensing our indecision, had decided that she no longer wished to breast-feed her infant.

What education should women new to breast-feeding receive before and after delivery? Our nursery and labor and delivery nursing staffs are uniformly supportive of women breast-feeding their infants, as is the prepartum maternal education staff. Women are urged to breast-feed, and a high percentage (about 75%) of women leave the hospital nursing their infants. They are given the telephone numbers of hospital staff members especially knowledgeable about breast-feeding to call should problems arise. Hospital stays here, however, as elsewhere, have continued to decrease after delivery, now averaging less than 24 hours for women after a vaginal delivery and less than 3 days for a woman who has had a cesarean delivery. This allows little time for education or for ensuring that breast-feeding is well established.

Because we have seen several cases such as this one, we have instituted a policy of telephoning all new mothers one to two days after discharge to attempt to detect situations where nursing problems are occurring. Our hospital has hired a certified lactation consultant to provide education and support to breast-feeding women and to head off impending problems such as this one.

The following guidelines have been published for detecting possibly hypernatremic dehydrated infants[7]: slow feeding, poor sucking; a sleepy, quiet, "good baby," causing parents to be unaware of evolving dehydration; and possibly diminished milk secretion. Our first face-to-face visit with new mothers is five to ten days after discharge; the presence of these findings or the irritability that others note in hypernatremic infants prompts the practitioner to ask the parent to bring the infant to the clinic earlier than this first scheduled visit.

How can we prevent possible disasters like this? Lacking the ability to keep women and their infants in the hospital long enough to observe breast-feeding adequately and to educate them fully regarding the signs of dehydration and hypernatremia, steps such as those referred to earlier are of considerable importance. More prenatal education, written information as to warning signs, follow-up calls, early postpartum visits, and round-the-clock availability of infant medical care may help. All of us—physicians, nurses, lactation consultants, and others—need to continue to make the case to all mothers that "breast is best," despite such rare, untoward events as this.[12]

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Lisinopril Therapy Associated With Acute Pancreatitis

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ACUTE PANCREATITIS has many causes, the most common being cholelithiasis and alcohol abuse.[1] Many other causes have been implicated, however, including abdominal trauma, metabolic derangements such as hypercalcemia and hypertriglyceridemia, anatomic abnormalities such as pancreas divisum, infections, hypoperfusion, idiopathic causes, and drugs. Drugs definitively associated with pancreatitis include sulfonamides, azathioprine, furosemide, estrogens, tetracycline, didanosine, and pentamidine. Many other drugs have been reported to cause pancreatitis, but they do not appear on textbook lists of commonly associated causes. Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension, heart failure, and diabetic nephropathy, is not usually considered a cause of pancreatitis, but recently a few isolated reports have suggested an association. We report the case of a man without any risk factors for pancreatitis in whom acute pancreatitis developed two weeks after lisinopril therapy was initiated for diabetic proteinuria.

Report of a Case

The patient, a 62-year-old man with a history of non–insulin-dependent diabetes mellitus, presented to the emergency department after one day of severe epigastric pain. He did not have nausea, vomiting, diarrhea, acholic stools, melena, or dysuria. He had no previous history of biliary tract disease or recent abdominal trauma. His medical history was notable for benign prostatic hypertrophy. He had had no abdominal operations. Two weeks before admission, he had begun taking lisinopril, 5 mg a day, for proteinuria. Other medications on admission were glyburide, 2.5 mg a day, a multivitamin, and one aspirin daily. He denied alcohol use, and he had no known drug allergies.

On physical examination, the patient was afebrile with a blood pressure of 181/86 mm of mercury, a pulse rate of 86 beats per minute, and respirations of 16 per minute. He was moving around the bed in discomfort. His abdomen was obese and soft without distention. There was tenderness to palpation in the epigastric area and left upper quadrant with no rebound or guarding. Bowel sounds were normoactive. There was no periumbilical or flank ecchymosis. A guaiac test of the stool was negative for occult blood.

Admission laboratory tests revealed a serum amylase level of 956 units per liter and a lipase level of 1,687 units per liter. The hematocrit was 0.46 (46%) with a leukocyte count of 13.7×10^9 cells per liter (13,700 cells per mm^3). Electrolyte values were normal, as were the blood urea nitrogen and creatinine levels. A serum glucose level was 9.5 mmol per liter (172 mg per dl). Liver function test values were normal. A serum calcium level was 2.32 mmol per liter (9.3 mg per dl), and the triglyceride level was 1.72 mmol per liter (153 mg per dl). A urinalysis showed only mild proteinuria. Ultrasonography of the abdomen revealed pancreatic inflammation with a normal gallbladder; there was no cholelithiasis or biliary dilatation.

The patient was admitted to the hospital with a diagnosis of acute pancreatitis, likely due to the use of lisinopril. The lisinopril therapy was discontinued, and he improved rapidly over the next few days, with the amylase and lipase levels decreasing to 87 and 27 units per liter, respectively, at the time of discharge. He has done well off lisinopril since discharge.

Discussion

Acute pancreatitis can present in a spectrum of mild disease to multisystem organ failure and death. There are many causes, with gallstones and alcohol abuse accounting for 80% of all cases in the United States and Western Europe.[1] The remaining 20% of cases are due to various other causes (Table 1).[1,2] The diagnosis of acute pancreatitis rests generally on increased levels of serum amylase and lipase. The lipase value may be more specific and sensitive because hyperamylasemia may occur in various other conditions[1]: small bowel obstruction, fallopian tube disease, parotid inflammation, renal failure, morphine administration, and macroamylasemia.[2,3(p791)] Ultrasonography is a useful adjunct in the diagnosis, with a sensitivity of 67% and a specificity approaching 100%.[1] Computed tomography and endoscopic retrograde cholangiopancreatography are also occasionally used in the diagnosis.

The pathogenesis of acute pancreatitis is similar despite the cause: inappropriate activation of digestive enzymes with autodigestion and the death of pancreatic tissue.[2] The activation of trypsin from trypsinogen is thought to be an early event in the pathogenesis.[1] Trypsin may spill into the bloodstream and cause many of the systemic complications of acute pancreatitis, including hypotension, shock, the adult respiratory distress syndrome, disseminated intravascular coagulation, and hypocalcemia.[2] Phospholipase A_2, elastase, complement, and kinins may also play a role in the systemic manifestations of acute pancreatitis.[1-3]

Many drugs are implicated as possible causes of acute pancreatitis (Table 2).[1,2] Although lisinopril is not listed as a possible cause of pancreatitis in recent review articles[1,4-6] and textbooks,[2] a handful of cases of acute pancreatitis have been linked to the use of lisinopril and

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other ACE inhibitors over the past several years. Enalapril and captopril have been reported as rarely causing acute pancreatitis.[7-9] Lisinopril has also been recently implicated as a possible cause of acute pancreatitis,[7,10] but few cases are found in the literature. Given the association in the literature of enalapril therapy with pancreatitis,[8,9] it is not surprising that an association may exist between the use of lisinopril and acute pancreatitis.

The pathophysiology of ACE inhibitor-induced pancreatitis remains speculative but has been proposed by some authors to be due to localized angioedema of pancreatic tissue with ensuing ductal obstruction.[7,9] Angiotensin-converting enzyme inhibitors have been associated with upper airway angioedema possibly due to altered bradykinin metabolism; this may also be the mechanism for pancreatic angioedema.[6] Also, ACE inhibitors can induce hypoglycemia, suggesting a directly toxic effect on pancreatic tissue.[8,11] Although some researchers have proposed the formation of autoantibodies by ACE inhibitors to pancreatic acinar cells,[12] the exact mechanism by which they may cause acute pancreatitis remains unknown.

A case of fatal pancreatitis was recently reported in a person taking lisinopril for ten months.[10] Another case was reported in which pancreatitis developed after two years of lisinopril therapy.[11] Our patient was also taking lisinopril, but therapy was initiated only two weeks before his symptoms began. This short time period strengthens the temporal association of lisinopril as a possible cause of this patient's pancreatitis. Also, after the drug was discontinued, our patient had rapid symptomatic and biochemical improvement, further supporting an association. When we contacted Zeneca Pharmaceuticals (manufacturer of Zestril), they noted only the isolated case reports in the literature and a few phone calls as evidence that lisinopril could be a possible cause of acute pancreatitis.

We cannot prove that lisinopril is the definite cause of acute pancreatitis in our patient, as we did not readminister the drug to see if the pancreatitis would recur. The temporal association of the initiation of the drug therapy with the patient's symptoms, the lack of other risk factors, and pronounced improvement without recurrence after lisinopril therapy was stopped all support the possibility that lisinopril caused his acute pancreatitis. Because of its modest cost, long half-life, low side-effect profile,[12] and many indications,[4,5] the use of lisinopril is likely to increase. As a result, clinicians need to be aware of the distinct possibility of acute pancreatitis when evaluating a patient taking lisinopril who presents with abdominal pain.

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Editorials

Asthma Therapy—Future Promise and Current Practice

THE CONVERGENCE OF findings from studies of the epidemiology, physiology, histopathology, and cell biology of asthma has transformed our conception of the disease. Epidemiologic studies have shown asthma to be an important cause of suffering, economic hardship, and death.[1,2] The National Institutes of Health and the pharmaceutical industry recognize that developing better treatments of asthma is worth the investment. Physiologic studies have shown that asthma is a chronic illness characterized by persistent bronchial hyperreactivity, even in patients who have only occasional symptomatic attacks. Histopathologic studies of the airways of patients dying of asthma and of patients with asthma mild enough to volunteer for bronchoscopy and bronchial mucosal biopsy show changes that differ only in degree: epithelial damage, deposition of collagen beneath the basement membrane, eosinophilic and lymphocytic infiltration of an edematous airway wall, and hypertrophy and hyperplasia of goblet cells, submucosal glands, and airway smooth muscle.[3,4] These structural changes do not have the look of abnormalities that are easily reversible, and "airway wall remodeling" is now considered an important consequence of chronic, poorly controlled asthma.[5] Studies using the tools of cell biology have at once shown that asthma may be fundamentally mediated by a difference in the type of lymphocytes predominating in the airway mucosa and may also involve bewilderingly complex interactions among resident and migratory cells.

The simplest interpretation of these studies is that asthma is a function of the sensitization of a subpopulation of $CD4^+$ lymphocytes, the Th-2 subtype, in the airways.[6,7] These lymphocytes produce a family of cytokines, including interleukins 3, 4, 5, 10, 13, and granulocyte-macrophage colony-stimulating factor, that favor immunoglobulin E production and the growth and activation of mast cells and eosinophils, arming the airways with the mechanisms of response to a subsequent reexposure to the allergen.

This interpretation is incomplete. It pays insufficient attention, for example, to evidence that mast cells and airway epithelial cells are themselves important sources of cytokines, and it does not account for attacks provoked by viral respiratory tract infections, the most frequent cause of asthma exacerbations. It nonetheless has served as a guide for future research on new therapies. Murine models of airway hyperreactivity that are characterized by antigen-induced Th-2 cell activation, the increased production of cell adhesion molecules in the bronchial vasculature, and an influx of eosinophils into the airways have been developed,[8] and the tools of monoclonal antibodies and genetic recombinant strains of mice, overexpressing or deficient in genes for specific cytokines, will likely define the essential elements in asthma's pathophysiology.

Although the current conceptual model has stimulated research along lines that will almost certainly lead to powerful new treatments, it has also put current therapies in a new light. Seeing asthma as an inflammatory disease associated with bronchial hyperreactivity clarifies that its treatment should involve the use of anti-inflammatory agents and drugs that relax airway smooth muscle. As anti-inflammatory agents that act in part by inhibiting the lymphocyte production of cytokines, corticosteroids would seem to be good candidates for asthma treatment, and the regular use of inhaled corticosteroids has indeed been shown to be highly effective in improving airflow, relieving symptoms, reducing bronchial reactivity, and preventing exacerbations.[9,10] The clinical benefit of inhaled corticosteroids appears to take time to develop. Depending on the end point studied, a plateau in the effect of a particular dose may not be seen for 6 to 12 months.[11] Several months' treatment with inhaled corticosteroids has also been shown to alter the pathologic changes of asthma, reducing epithelial damage and the numbers of eosinophils and mast cells in the mucosa, and even partly reversing the deposition of collagen beneath the basement membrane.[12] This last finding, that inhaled corticosteroids may reverse fibrotic changes in the airway wall, is supported by recent, preliminary findings that the best achievable pulmonary function is lower in patients for whom inhaled corticosteroid therapy is delayed when compared with matched subjects in whom therapy was started early.[13] It is thus possible that inhaled corticosteroids may be effective not only in improving asthma control but also in reducing the chance of the development of severe, irreversible airflow obstruction, the fate of a small proportion of persons with chronic asthma.

As effective as they are in improving asthma control while they are taken, inhaled corticosteroids are not curative. Even after prolonged treatment, asthma symptoms return in most patients when inhaled corticosteroids are withdrawn.[14] And even in patients with mild asthma, inhaled corticosteroid treatment reduces, but does not eliminate, asthma symptoms. The additional use of bronchodilators is necessary, and inhaled β-agonists are the most effective of those available. Taken immediately, inhaled β-agonists act promptly and produce few systemic side effects. The issue in the use of β-agonists does not have to do with their immediate efficacy or toxicity, for they are safe and effective, even lifesaving, when taken for the relief of bronchoconstriction; rather, it has to do with their long-term toxicity. Case-controlled studies from New Zealand and Canada suggest that the excessive use of inhaled fenoterol, a β-agonist not used in the United States, was strongly asso-

ciated with the risk of fatal or near-fatal attacks of asthma; the excessive use of albuterol was found to have a similar but weaker association.[15] A controlled study of the effects of the regular use of fenoterol versus placebo showed worsened asthma control with the active treatment.[16] Finally, several studies have shown that a regular use of β-agonists leads to the loss of their ability to protect against the bronchoconstriction provoked by methacholine, exercise, and antigen inhalation.[17]

The stakes in resolving the question of possibly harmful effects of the regular use of inhaled β-agonists have been raised by the introduction of salmeterol, a very-long-acting inhaled β-agonist, into the United States market. So far, fears that its use might lead to an increase in the frequency or severity of attacks of asthma seem unfounded, and two large studies comparing the regular use of salmeterol with the regular use of albuterol and of placebo not only show salmeterol to be most effective in improving asthma control but also fail to show any adverse effect of the regular use of albuterol versus placebo.[18,19] In patients with asthma inadequately controlled with the use of inhaled corticosteroids, the addition of twice-a-day inhalations of salmeterol has been shown to be superior to doubling the dose of the inhaled corticosteroid.[20]

The implications of the findings of basic research on the pathophysiology of asthma and of clinical research on asthma treatment are concordant. For patients with more than mild asthma, the regular use of an inhaled corticosteroid and the as-needed use of an inhaled β-agonist are effective and safe. Concerns over possible long-term toxicity of the systemic absorption of an inhaled corticosteroid seem unfounded, at least so long as the total dose of inhaled corticosteroid is less than 800 to 1,000 μg per day for adults and less than 400 μg per day for children. For patients inadequately controlled on standard doses of those medications, the addition of the regular use of salmeterol seems likely to be more effective than increasing the dose of the inhaled corticosteroid.

The major features of these recommendations for asthma treatment, described in detail by Kleerup and Tashkin in this issue,[21] have been endorsed by consensus groups and expert panels around the world. Their validity is not immutable. The results of large, ongoing prospective studies on the effects of regularly inhaled β-agonists or corticosteroids may cause a reassessment of their place in treatment. New inhaled corticosteroid preparations with greater local potency and less systemic absorption are about to be released,[22] and other, completely novel therapies with more precise mechanisms of action are under development. For the small proportion of asthmatic patients whose disease is not controlled by current treatments, the future holds hope. In the meantime, our obligation as a healing profession is to be certain that these patients understand the nature of their disease, the purposes of their treatments, the availability of tools for self-monitoring, and the instructions for seeking a higher level of care. This obligation, no less than the prescription of effective and safe medications, is properly emphasized in Kleerup and Tashkin's review.

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Sinusitis—Beginning a New Age of Enlightenment?

THE PARANASAL SINUSES were first described by Leonardo da Vinci in the publication "Two Views of the Skull." Since his description, numerous theories have been espoused on the anatomical or physiologic impor-

tance of the sinuses in humans. These include insulation, reducing cranial weight, heating and humidifying the air, imparting resonance to the voice, and simply to replace functionless bone. Despite the proliferation of theories, their functional role remains a mystery. Less mysterious to millions of patients is the misery associated with their diseased sinuses. In fact, some have argued that this evolutionary legacy has "proved much more of a liability than an asset as no other species has the misfortune to suffer from sinusitis or other allied respiratory problems."[1(p214)]

Although the function of the paranasal sinuses is unclear, our understanding of the epidemiology, pathophysiology, and treatment of sinusitis is advancing. As pointed out by Reuler and co-workers elsewhere in this issue, sinusitis is one of the most prevalent disorders encountered in general medical practice.[2] In the 1992 National Ambulatory Medical Survey, sinusitis was the fifth most common diagnosis for which an antibiotic was prescribed, an increase of almost 80% over three years previously.[3] Similarly, the 1992 National Health Review Survey showed that the prevalence rate for sinusitis (146 per 1,000 population) exceeded that of any other reported chronic condition.[4]

Why is sinusitis so prevalent, and why is its prevalence apparently increasing? It is tempting to speculate that the observed rise in prevalence is related to a rise in predisposing factors. For example, an increasing number of Americans are living in metropolitan areas characterized by poor air quality and nasal irritants. Further, higher population density is known to enhance the spread of infectious diseases such as viral rhinitis, a frequent antecedent of acute sinusitis. Alternatively, the rising prevalence of sinusitis may be more apparent than real and be related to better diagnostic modalities. Fiberoptic rhinoscopy allows direct visualization of diseased sinus mucosa, and its use may lead to an increased detection of occult or chronic diseases. Computed tomography (CT) and nuclear magnetic resonance imaging are much more sensitive to mucosal changes than standard "plain film" radiographs. In a recent investigation, 87% of subjects with community-acquired colds had CT evidence of maxillary sinusitis, findings that resolved spontaneously in most of the subjects. Therefore, CT may be too sensitive for the purpose of determining who needs treatment. In any case, an increased recognition of sinus disease, including subclinical cases, rather than an increased incidence of the disease, may explain the rising prevalence.

Whether a real phenomenon or simply an artifact of changing diagnostic technology, the surge in cases of sinus disease is associated with a large number of patient visits and increased health care expenditures. Each year, patients make 16 million physician visits and spend more than $2 billion on over-the-counter medications in pursuit of symptomatic relief of sinus disease. These statistics alone reflect the substantial morbidity of sinusitis. Despite the high prevalence of disease and its associated morbidity and health care costs, our knowledge base is meager as relatively few original investigations have been published on sinusitis in recent years. Further studies are needed to better define the epidemiology of acute sinusitis and to guide prevention strategies. Can acute sinusitis be prevented by using nasal corticosteroids to more aggressively manage allergic rhinitis? Is sinusitis averted by the prompt use of nasal decongestants for sufferers of the common cold? Should patients with viral rhinitis avoid the use of antihistamines (including scores of over-the-counter medications) that theoretically may predispose to sinusitis by thickening secretions and decreasing sinus drainage? All of these practical treatment issues need to be addressed in sound clinical investigations.

The diagnosis of sinusitis also needs attention. For acute sinusitis, the clinical evaluation has been shown sufficient for diagnosis in most patients. General internists diagnose acute sinusitis with about 75% accuracy, and a recent decision analysis suggests probability thresholds for empiric treatment or diagnostic testing. This decision strategy has not been validated, however, and should be examined to see if it improves patient outcomes. In the initial treatment of acute disease, therapeutic regimens that include antibiotics plus decongestants lead to good clinical response rates. Solitary studies on the role of ancillary therapies such as guaifenesin, niflumic acid (a nonsteroidal anti-inflammatory drug tested in Europe), and nasal corticosteroids suggest possible benefit, but further study is needed. Because the overall response rate is high, studies will be needed to determine if therapies reduce the intensity and duration of symptoms and should include long-term follow-up to assess relapse rates.

Although first-line therapy is effective for most primary care patients with acute sinusitis, 10% to 25% of patients have persistent symptoms that require a second course of therapy. For these patients, the most cost-effective diagnostic and therapeutic approach is yet to be determined. In my general medical practice, I confirm the diagnosis with a single Waters' view radiograph before prescribing an extended course of a broad-spectrum antibiotic plus decongestants. Others treat empirically or obtain a sinus CT to better examine the sinuses before treating further.

In population-based surveys, the prevalence of chronic sinusitis far exceeds that of acute sinusitis, and it is in this realm that some of the most important recent advances have been made. Sinus CT has increased greatly our understanding of the anatomic changes in chronic sinusitis and guided the development of new surgical interventions. It has shown that the ostiomeatal complex, an area at the confluence of drainage from the frontal, maxillary, and anterior ethmoid sinuses, is usually diseased in chronic sinusitis. Studies in animals have shown that poor sinus drainage is the seminal event that precipitates acute infection, and it is thought that the mucosal changes of chronic sinusitis are due to persistent obstruction. Functional endoscopic sinus surgery is directed at restoring physiologic sinus drainage by removing diseased mucosa in the ostiomeatal complex. Case series have shown a high response rate, although outcomes have not been

measured rigorously, and there are no randomized trials comparing this surgical therapy with aggressive medical management. Because endoscopic sinus operations are expensive and carry a small risk of serious complications, this unproved but promising treatment option deserves further study.

The evolutionary impetus behind the development of the paranasal sinuses may never be fully understood. But we are poised to enter a new age of enlightenment about the diagnosis and management of the diseased sinuses. Advanced imaging procedures, fiberoptic visualization, and an improved array of pharmacologic and surgical treatments should catalyze our understanding of sinus disorders. The important next step is to design and carry out clinical trials to determine how each of these resources is optimally used to improve patient outcomes in a cost-effective manner.

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Correspondence

Late HIV Diagnosis

To the Editor: The early diagnosis of infection with the human immunodeficiency virus (HIV) provides the potential for several benefits. Persons diagnosed at an early stage of HIV infection can receive more timely medical care, along with psychosocial support services and preventive interventions.[1,2] In addition, knowledge of one's infection can be an incentive to take precautions to prevent transmitting HIV to others and to notify those who may have already been exposed.[3]

As part of an ongoing interview project sponsored by the Centers for Disease Control and Prevention,[4] we obtained information on the date of a first-positive HIV antibody test and the reasons for seeking testing among a sample of 678 (89%) men and 82 (11%) women who were reported to the Los Angeles County acquired immunodeficiency syndrome (AIDS) surveillance registry between January 1990 and July 1994. The median time interval from a first-positive HIV test to a diagnosis of AIDS was 14 months. This interval did not vary by sex (14 months for both men and women) but did vary by race or ethnicity (8 months for both blacks and Latinos compared with 32 months for whites), education level (8 months for those who had not completed high school, 13 months for high school graduates, 15 months for those with some college, and 29 months for college graduates), and risk group (6 months for persons reporting heterosexual risk, 13 months for men reporting sex with men, 19 months for persons reporting injection-drug use, and 23 months for men reporting sex with men and injection-drug use). The racial or ethnic variation found in the total group was evident in each education stratum.

Almost half (46%) of those interviewed reported that the main reason they sought HIV testing was because they were ill (Figure 1). Only 26% of men and 24% of women reported that their primary reason for seeking testing was that they believed they were at risk of infection.

Given an estimated median incubation period for AIDS of about ten years,[5] these data suggest that many persons reported with AIDS in Los Angeles County during 1990 to 1994 were unaware of their infection until relatively late in their disease course. A late diagnosis was especially common among blacks, Latinos, persons with less education, and persons reporting sexual activity as their only HIV risk. Of particular concern is that many respondents reported not seeking testing until they were ill.

Although these data were collected from persons reported with AIDS and, thus, may not be representative of all those infected with HIV, the findings highlight the need for increased efforts to ensure early diagnosis and referral for services among those who are infected. Individual and institutional barriers to HIV antibody testing must be identified and efforts made to reduce or eliminate them. Essential to this process is a commitment to ensuring that all persons who are HIV infected have access to needed services and that adequate legal safeguards are in place to protect against discrimination.

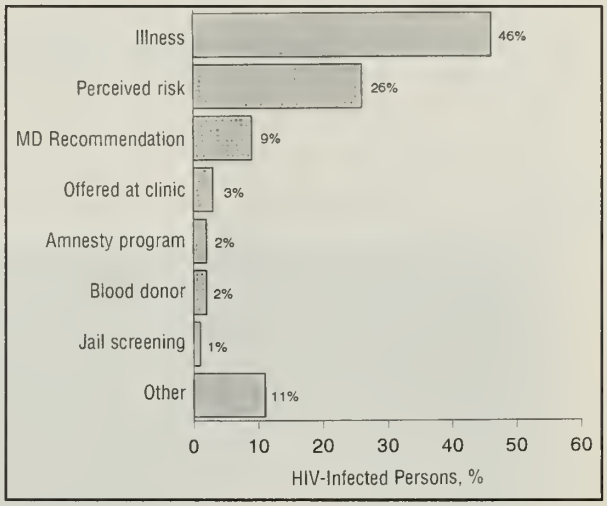

Figure 1.—The graph illustrates the primary reason given for seeking human immunodeficiency virus (HIV) testing among persons reported with the acquired immunodeficiency syndrome in Los Angeles County, January 1990 to July 1994 (n = 760).

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Commentary

What the Artist Sees and Paints

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Figure 1.—A painting by Goya shows the Infanta Maria Josefa with what appears to be a melanoma.

(White LP: What the artist sees and paints. West J Med 1995; 163:84-85)

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In the years 1800 to 1801, Francisco de Goya painted a large group portrait of the family of King Charles IV of Spain. Included in this group is the king's sister, the Infanta Maria Josefa, aged 56 years. On her right temple is a large, black tumor, probably a melanoma, arising in what was surely a lentigo maligna.[1] One can see the raised edges of this tumor.[2] It is reported that the Infanta died of unspecified causes six months after the painting was completed. For several reasons the cause of her death is speculative and not certain.

Artists often see and paint reality before physicians or scientists recognize reality.[3]

Melanoma is an old and familiar disease. Hippocrates was said to have described it, but he did not. He must have seen it. It was first recognized as cancer in 1781; Gioanni Carlo Brugnone, a veterinarian in Torino, Italy, described the condition in horses, usually old gray horses.[4] It was first recognized as a distinct cancer in humans by René Laënnec in 1807,[5] although Everard Home in 1805 described a number of cases of cancer,[6] one of which was shown years later to have been a melanoma. The introduction of the use of the light microscope in pathology in the middle of the 19th century began the modern delineation of melanoma in humans.[7,8]

One of the reasons Goya is one of the world's great painters is that he painted portraits, blemishes and all. In this instance he appears to have painted a royal princess, cancer and all. Most artists covered over the spots and showed us in their finished works only cleaned-up versions. Goya was different. It appears that he painted a portrait of a woman with a melanoma six years before one of our most careful and important physicians first described the disease.

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* * *

Scrutability

Tu Fu, old and ravaged by consumption,
bent over his mulberry paper and wrote
the characters "single" and "wild goose,"
his eyes weakened by the moonlight.

Because it was October in his life,
he refilled his cup with wine.
His joys were neither large nor many.
But they were precise.

SAM HAMILL©
Port Townsend, Washington

Lessons From the Practice

Medicine's Achilles' Heel

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As a local public health pediatrician, I was invited to a meeting with the parents of a child who had suffered a severe adverse reaction to a DPT [diphtheria-pertussis-tetanus] vaccine shot, as acknowledged by a "Special Master" of the US Department of Justice.

A day after her first DPT vaccination, the 18-month-old girl seemed unsteady and slurred her speech. Two days following the vaccine, there was no doubt that something was terribly wrong. Over the following days, she became unable to stand or hold up her head. Her eyes crossed, and she began convulsing. A diagnosis of acute cerebellar ataxia was ultimately made and confirmed by a tertiary care center neurologist. The cause was postviral. Today, at 7 years of age, this youngster works through 14 physical and speech therapy sessions a week, though she is much improved and continues progressing. She can speak, walk, run, and play, but is still in the process of restoring hope to the family.

The parents told me that they had been distressed and actually felt humiliated by physicians who refused to even consider the possibility that their daughter's symptoms had been caused by the vaccine. They were not anti-medical establishment crusaders nor were they opposed to vaccines. Both were college educated, articulate, and personable. They postulated that if most physicians respond similarly, substantial underreporting of vaccine-related events must be occurring, despite the legal requirement for reporting. The statistics on which parents and health professionals base their opinions could be skewed.

Their child's case had never been reported, despite the onset of her symptoms within 18 hours of receiving the vaccine. Numerous pediatricians, neurologists, and other specialists had been consulted. The reporting requirement applies only to the onset of symptoms within a specified time frame and does not ask for proof or even a reasonable certainty of cause. Why might physicians deny the possibility of a vaccine reaction?

I have administered thousands of DPT vaccines. I have a daughter who received the same shot in the same clinic at the same age as this child. What do I have to know and believe to place myself in such a position of responsibility and vulnerability? I am committed to understand, as accurately as current scientific evidence will permit, what will be helpful and harmful to my child and to my patients. Yet I must accept a certain scientific uncertainty. I cannot know everything or predict an outcome in an individual case.

Certain scientific evidence is available to me. We have all been taught that events associated closely in time are not necessarily related as cause and effect. Well-researched and accepted ongoing studies show insufficient epidemiologic evidence that either favors or rejects a causal relationship between DPT vaccination and chronic neurologic damage, though evidence so far is consistent with a causal relation with acute encephalopathy. Acute cerebellar ataxia is not mentioned specifically in the summary studies.

I was concerned, though, that more than scientific considerations were behind the physicians' reactions to this child's predicament—perhaps their fear of being held responsible, their inability to tolerate lack of certainty, or simply the difficulty of facing the parents of a child who might have been harmed, however unlikely the statistical probability, by one's own medical treatment. Do some physicians simply deny the possibility of an adverse outcome so that they can continue to function confidently?

The feelings described by these parents reflect, I think, their reaction to the underlying attitudes of their physicians, though the physicians never verbalized those attitudes. As the child's condition deteriorated, very little could have been done to comfort these parents. Yet the confident stance of the medical community, rather than being reassuring, left the parents feeling betrayed. These physicians' attitudes contributed to the inaccuracy of the present reporting system, as well as to the suffering of the parents.

As a physician, I aspire to be an empathic scientist. To be a scientist, to strive to narrow the gap between what is considered scientific fact and what is yet to be learned from experience, there must remain, despite fatigue and perhaps overwhelming contradictory evidence, a glimmer of curiosity and a willingness to accept new or unexpected information. To be empathic, physicians must maintain that emotional Achilles' heel, the sense of responsibility for harming a patient while having the best of intentions. Sometimes the weight falls on that heel, and it is painful.

(Malinoff FJ: Medicine's Achilles' heel. West J Med 1995; 163:86)

Dr Malinoff is Family Services Medical Director of the County of Santa Barbara Health Care Services, Santa Barbara, California.
Reprint requests to Frances J. Malinoff, MD, County of Santa Barbara Health Care Services, 315 Camino del Remedio, Santa Barbara, CA 93110.

(Continued from Page 16)

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 24-28—**Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center. Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 27-29—**15th Annual Montgomery Dorsey Symposium: The Fate of the American Health Care System.** HealthOne Foundation at the Hyatt Regency, Bever Creek. Thurs-Sat. Contact: Khanh Ngugen, (303) 322-1523 or (800) 933-3955.

July 28-August 1—**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

July 31-August 4—**21st Annual Dynamic Psychotherapy Program: Gender Issues and Dynamic Psychotherapy**. University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 1-5—**Basic Course in Otolaryngic Allergy.** American Academy of Otolaryngic Allergy at Hyatt Regency, Denver. Tues-Sat. Contact: Zev Lewis, AAOA, (301) 588-1800.

August 3-6—**Cardiovascular Interventions: Technology at The Summit V**. University of Colorado Health Sciences Center at Aspen. Thurs-Sun. Contact: U of Colo.

August 10-13—**Fifth Annual Women Physicians: Finding a Balance Conference.** Rose Medical Center at Vail. Thurs-Sun. Contact: Ann Wilcox, (800) 525-1253 or (303) 320-2102.

August 11-13—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass. Fri-Sun. Contact: U of Colo.

August 13-18—**20th Annual Primary Musculoskeletal Care Conference.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

September 8-9—**Alzheimer's Disease Update for Physicians.** University of Colorado Health Sciences Center at Red Lion Inn, Denver. Fri-Sat. Contact: U of Colo.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Medical Education, Primary Children's Medical Center, Salt Lake City, at Sun Valley Resort, Sun Valley. Fri-Sun. Contact: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City, UT 84113. (801) 588-2000.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 21-23—**How to Diagnose and Treat Arrhythmias for the Primary Care Physician.** New Mexico Heart Institute at the Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Megan Slane, NM Heart Institute, 1001 Coal SE, Albuquerque 87106. (505) 841-1000 or (800) 888-6642.

August 3-6—**Sport Medicine and Imaging**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 7-8—**Pediatrics for the Practitioner—Back to the Basics**. New Mexico Pediatric Society at the Roswell Inn, Roswell. Sat-Sun. Contact: Steve Yabek, MD, NM Pediatric Society, 715 Grand Ave NE, Ste 207, Albuquerque 98102. (505) 848-3700.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

October 27-28—**ECG, Interpretation for the Primary Care Physician.** New Mexico Heart Institute at the Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, NM Heart Institute, 1001 Coal SE, Albuquerque 87106. (505) 841-1001 or (800) 888-6642.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Contact: Billie Dytzel, (505) 265-0732.

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CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Education at Sun Valley Resort, Sun Valley, Idaho. Fri-Sun. Contact: PCMC.

October 27-29—**Intensive Interactive Head and Neck Imaging Course.** University of Utah at Marriott Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-4060.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 20-23—**Comprehensive Review in Toxicology.** Tacoma. Thurs-Sun. Contact: Madigan Army Medical Center, (206) 968-0118.

July 31-August 5—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 4-5—**Otolaryngology Update.** Tacoma. Fri-Sat. Contact: Madigan Army Medical Center, (206) 968-0118.

August 17-18—**CME Networking in the Northwest**. Port Ludlow. Contact: Valley Medical Center, (206) 575-4721.

August 22-25—**Trauma Radiology: 1995**. Seattle. Tues-Fri. Contact: IMM, (713) 965-0566.

September 9-13—**Intensive Training Workshop in Dialectical Behavior Therapy**. Seattle. Sat-Wed. Contact: U/W, (206) 543-9886.

September 11-15—**23rd Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 14-16—**Symposium on Teaching Internal Medicine.** Seattle. Thurs-Sat. Contact: U/W.

September 22-23—**Laparoscopic Surgery: Upper GI.** Seattle. Fri-Sat. Contact: U/W.

September 28—**Infectious Disease Conference.** Renton. Thurs. Contact: Valley Medical Center, (206) 575-4721.

October 6—**John Locke Cardiology.** Seattle. Fri. Contact: Swedish, (206) 386-2265.

October 6-7—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Fri-Sat. Contact: U/W.

October 21—**Practical Pediatrics.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

October 21-22—**ACLS.** Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

October 26-27—**Current Concepts in Drug Therapy**. Seattle. Thurs-Fri. Contact: U/W.

October 27—**7th Annual Current Concepts in Perinatology**. Tacoma. Fri. Contact: Multicare, (206) 552-1221.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 88)

November 3—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

November 10-11—**6th Annual Regional Conference for Occupational Therapy and Physical Therapy.** Seattle. Fri-Sat. Contact: U/W.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

November 16-18—**Surgery Update**. Seattle. Thurs-Sat. Contact: U/W.

November 17—Pinkham Basic Science Lectureship. Seattle. Fri. Contact: Swedish, (206) 386-2265.

November 24—**Urology Update.** Seattle. Fri. Contact: VMMC.

December 1—**Pediatrics Update**. Seattle. Fri. Contact: VMMC.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference**. Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

August 11-13—**Family Medicine Update.** Creighton University School of Medicine at Cheyenne. Fri-Sun. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 N 30th St, Ste 2130, Omaha, NE 68131.

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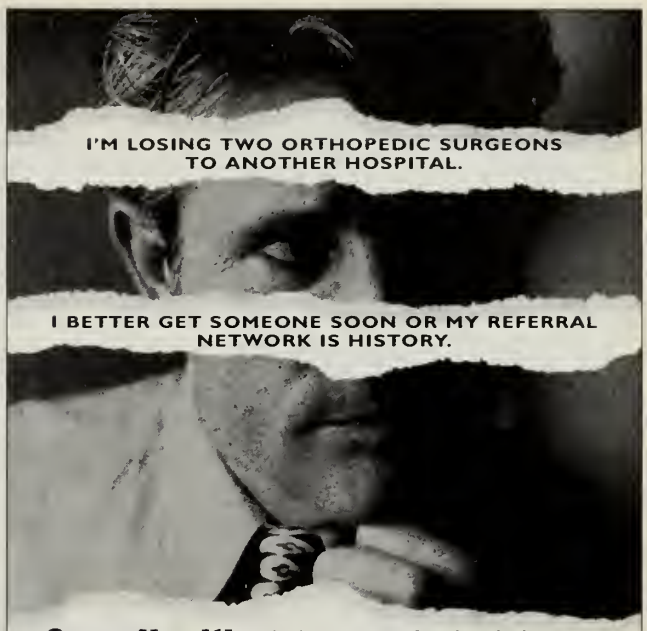

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Kaiser Permanente's Occupational Health Program in the Northwest Region (Oregon/Washington) has a total of 19 physicians and covers outpatient clinics at eight sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees.

We offer a competitive salary and benefits package which includes two comprehensive pension plans, paid professional liability, sabbatical leave and more. Please forward CV to: **W.J. Weiland, M.D., Regional Medical Director, Northwest Permanente, 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099.** EOE.

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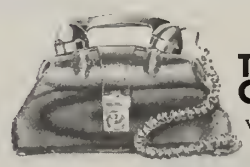

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Arizona Medical Association, Inc–810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1996, Scottsdale Plaza Resort, Scottsdale.

California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 1-5, 1996, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 27-30, 1995. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 28-30, 1995. Spokane Sheraton Hotel, Spokane, Washington.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 6-8, 1996, Jackson Lake Lodge, Moran.

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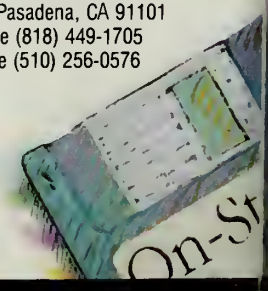

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The Western Journal of Medicine

VOLUME 163 • NUMBER 2 AUGUST 1995

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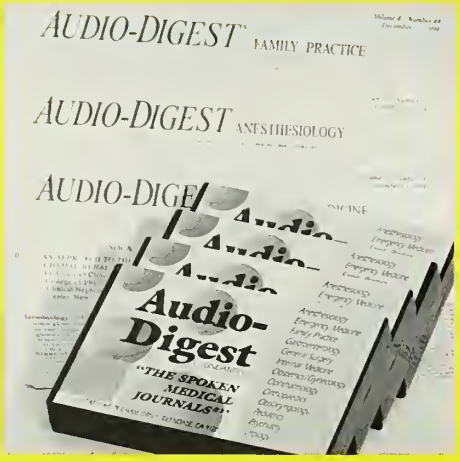

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The Western Journal of Medicine®

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Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style appears in most issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

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In Memoriam

California Medical Association

Brandman, Leonard J., San Diego. Died May 5, 1995, aged 78. Graduate of University of Michigan Medical School, Ann Arbor. Dr Brandman was a member of the San Diego County Medical Society.

Crippen, Kenneth D., San Diego. Died May 16, 1995, aged 71. Graduate of Medical College of Virginia, Richmond, 1952. Licensed in California in 1954. Dr Crippen was a member of the San Diego County Medical Society.

Dorsey, Thomas J., Orange. Died May 16, 1995, aged 70. Graduate of University of Iowa College of Medicine, Iowa City, 1952. Licensed in California in 1953. Dr Dorsey was a member of the Orange County Medical Association.

Elgin, James C., Boulder Creek. Died May 7, 1995, aged 82. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1940. Licensed in California in 1940. Dr Elgin was a member of the Santa Cruz County Medical Society.

Fowler, Frederick C., Bakersfield. Died Jun 24, 1995, aged 91. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Fowler was a member of the Kern County Medical Society.

Golden, Jerome A., Hemet. Died Mar 3, 1995, aged 72. Graduate of University of Colorado School of Medicine, Denver, 1950. Licensed in California in 1956. Dr Golden was a member of the Riverside County Medical Association.

Hall, Winston C., San Diego. Died May 1, 1995, aged 78. Graduate of University of Michigan Medical School, Ann Arbor, 1942. Licensed in California in 1949. Dr Hall was a member of the San Diego County Medical Society.

Harris, Thomas A., Sacramento. Died May 4, 1995, aged 85. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1940. Licensed in California in 1954. Dr Harris was a member of the Sacramento-El Dorado Medical Society.

Hartwell, Brace F., Santa Ana. Died May 6, 1995, aged 83. Graduate of George Washington University School of Medicine, Washington, DC, 1941. Licensed in California in 1942. Dr Hartwell was a member of the Orange County Medical Association.

Lavin, Sheldon E., Tarzana. Died May 4, 1995, aged 66. Graduate of University of Illinois College of Medicine, Chicago, 1953. Licensed in California in 1956. Dr Lavin was a member of the Los Angeles County Medical Association.

Letson, Frank C., San Bernardino. Died May 26, 1995, aged 62. Graduate of University of Kansas School of Medicine, Kansas City, 1962. Licensed in California in 1963. Dr Letson was a member of the San Bernardino County Medical Society.

Maloney, Basil W., La Mesa. Died May 4, 1995, aged 76. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1946. Licensed in California in 1954. Dr Maloney was a member of the San Diego County Medical Society.

Morris, Robert R., Green Valley, Arizona. Died May 3, 1995, aged 76. Graduate of Loma Linda University School of Medicine, Los Angeles, California, 1947. Licensed in California in 1947. Dr Morris was a member of the Humboldt-Del Norte Medical Society.

Parke, Fred F., San Bernardino. Died May 23, 1995, aged 85. Graduate of Northwestern University Medical School, Chicago, Illinois, 1942. Licensed in California in 1957. Dr Parke was a member of the San Bernardino County Medical Society.

Ryan, Edward J., Cupertino. Died Apr 2. 1995, aged 80. Graduate of Queens University Faculty of Medicine, Kingston, Ontario, 1938. Licensed in California in 1945. Dr Ryan was a member of the Orange County Medical Association.

Slaughter, Donald E., Napa. Died May 9, 1995, aged 74. Graduate of Stanford University School of Medicine, Stanford, California, 1953. Licensed in California in 1953. Dr Slaughter was a member of the Napa County Medical Society.

Tiss, George J., Visalia. Died Jun 21, 1995, aged 70. Graduate of University of Oregon Medical School, Portland, 1954. Licensed in California in 1957. Dr Tiss was a member of the Tulare County Medical Society.

Wells, Clifford S., Sacramento. Died May 27, 1995, aged 87. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Wells was a member of the Sacramento-El Dorado Medical Society.

Williams, Robert L., San Diego. Died May 20, 1995, aged 82. Graduate of Emory University School of Medicine, Atlanta, Georgia, 1936. Licensed in California in 1937. Dr Williams was a member of the San Diego County Medical Society.

Wright, Byron A., La Jolla. Died Apr 20, 1995, aged 81. Graduate of University of Southern California School of Medicine, Los Angeles, 1955. Licensed in California in 1956. Dr Wright was a member of the San Diego County Medical Society.

New Mexico Medical Society

Abshere, Lynn W., Clovis. Died Jan 19, 1995, aged 67. Graduate of University of Oklahoma School of Medicine, Oklahoma City, 1956. Licensed in New Mexico in 1961. Dr Abshere was a member of the Curry-DeBaca-Roosevelt Medical Society.

Antonio, Locksley B., Albuquerque. Died Apr 23, 1995, aged 70. Graduate of University of Berne, Switzerland, 1958. Licensed in New Mexico in 1980. Dr Antonio was a member of the Greater Albuquerque Medical Association.

Frerkes, Joseph L., Albuquerque. Died Apr 13, 1995, aged 45. Graduate of Loyola-Stritch School of Medicine, Maywood, Illinois, 1975. Dr Frerkes was a member of the Greater Albuquerque Medical Association.

Wyoming Medical Society

Thiel, Terrance J., Rock Springs. Died Jun 27, 1995, aged 45. Graduate of University of Minnesota. Licensed in Wyoming in 1994. Dr Thiel was a member of the Sweetwater County Medical Society.

The Western Journal of Medicine

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

In the battle against allergic rhinitis

A FIRST LINE OF DEFENSE

Symptomatic relief superior to QD non-sedating antihistamines[1,2]

See charts on reverse side

QD staying power

Convenient once-daily dosing for better compliance

Onset of action as early as 12 hours[3]

Maximum benefit is generally seen within 3 to 4 days[3]

Excellent safety profile

No measurable effect on HPA function at recommended doses[4,5]

The most commonly reported side effects are headache and nasal irritation, each with an incidence comparable to placebo

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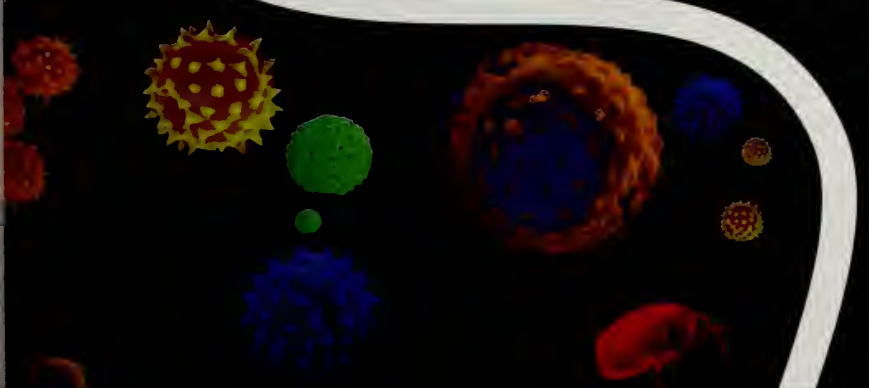

Please see brief summary of prescribing information on following page.

ONCE DAILY Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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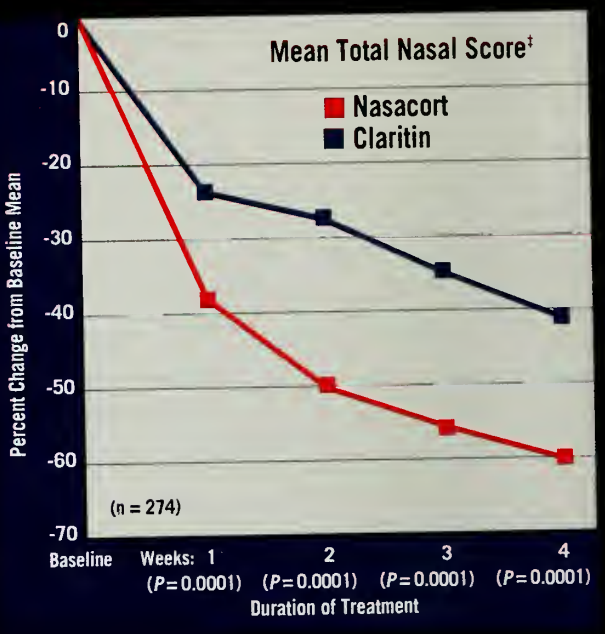
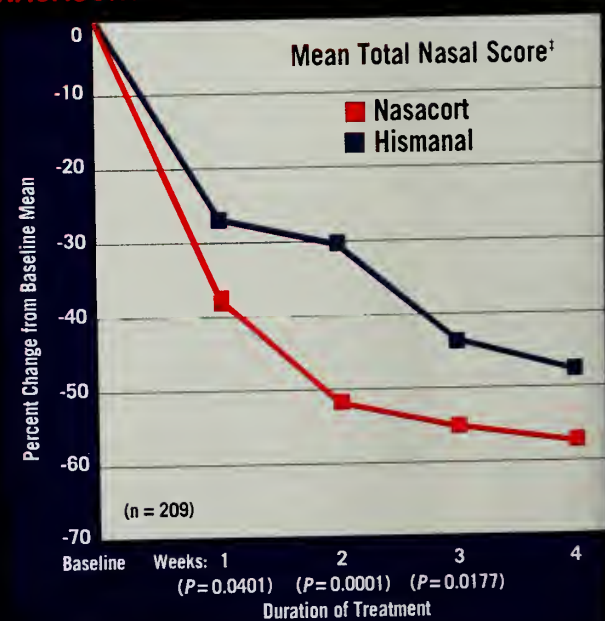
NASACORT VS. CLARITIN[1]*



‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[2]§



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*

† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*

§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

REFERENCES

1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom O, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 9—**Pain Management Collaborative.** Maricopa Medical Center at Hotel Park Tucson. Sat. Contact: (602) 267-5366.

September 9-October 14—**Managed Care Institute**. Samaritan Health System at the Buttes Resort, Tempe. Sats. Contact: Linda Luzader, (602) 495-4936.

September 20—**Crucial Issues for the Primary Care Physician—Infections Etc.** Maricopa Medical Center and Mayo Clinic Scottsdale at the Camelback Marriott, Phoenix. Contact: (602) 267-5366.

October 27-28—**Ethics in Managed Care Conference.** Samaritan Health Services at the Buttes Hotel, Phoenix. Fri-Sat. Contact: Linda Luzader, (602) 495-4936.

November 2-4—**Eighth Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 5—**Career Choices.** American College of Physician Executives at the Westin La Paloma, Tucson. Sun. Contact: (800) 562-8088.

Noveber 6-10—**Physician in Management Seminar I.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 6-10—**Physician in Management Seminar II.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 12-16—**5th Annual Psychopharmacology Review.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 16—**Nurture vs. Nature: An Implication for the 21st Century.** Los Angeles Society of Allergy, Asthma and Clinical Immunology at Peninsula Hotel, Beverly Hill. Sat. 8 hrs. Contact: Diann Smith, LASAACI, P O Box 84443, Los Angeles 90073. (818) 702-0459.

September 30—**Contemporary Management of Sinusitis**. UCSF at Laurel Heights Auditorium, San Francisco. Sat. Contact: UCSF.CME Listing - August 1995

January 30-February 3— **34th Annual Scientific Session of the Western Society of Allergy and Immunology**. Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, P.O. Box 1122, Roanoke, TX 76262. (817) 491-2616.

ANESTHESIOLOGY

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $285. Contact: CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

October 29-November 4—**Hawaiian Seminar on Clinical Anesthesia**. California Society of Anesthesiologists at Hyatt Regency Poipu Beach, Kauai, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

November 3-5—**Anesthesiology Update: 1995**. UCD at Monterey Plaza, Monterey. Fri-Sun. 12 hrs. $300. Contact: UCD.

January 11-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. 2 wks. 20 hrs. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City, CA 94404. (800) 345-3691.

CARDIOLOGY

October 5-7—**Cardiology Update—1995.** UCSF at Carmel Valley Ranch Resort, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

October 19-22—**Coronary Interventions 1995.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines, San Diego. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 28—**Update in Electrocardiography and Arrhythmias**. UCSF at Ana Hotel, San Francisco. Sat. 8 hrs. $150. Contact: UCSF.

November 18—**14th Annual Sharrer Symposium: Progress in Cardiology**. Kaweah Delta Hospital District at Visalia Convention Center. Sat. 6 hrs. Contact: Barbara Porter, RN, (209) 625-7106.

December 9—**Cardiac Therapeutics.** USC at Ritz-Carlton, Laguna Niguel. Sat. 8 hrs. $75. Contact: USC.

DERMATOLOGY

September 14-17—**3rd International Symposium on Cutaneous Fungal, Bacterial, and Viral Infection and Therapy**. UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sun. 24 hrs. $395. Contact: UCSF.

October 14-15—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. Contact: UCSF.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 109)

EMERGENCY MEDICINE

September 22—**Advanced Burn Life Support.** Torrance Memorial Medical Center. Fri. 9 hrs. $220. Contact: Nancy Wise, Torrance Memorial Burn Center, 3330 Lomita Blvd, Torrance 90505. (310) 517-4605, ext. 7607.

October 13-15—**Advances in Emergency Medicine.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 30-November 3—**24th Annual Topics in Emergency Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

November 11-12—**Biomechanics of Trauma**. UCSD at Le Meridien Coronado. Sat-Sun. 11 hrs. $200. Contact: UCSD.

November 13-17—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 3-8—**16th Annual Current Concepts in Emergency Care**. American College of Emergency Physicians at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269.

December 11-15—**Emergency Medicine Symposium II**. UCSD at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

September 22-24—**HIV, AIDS and Women**. UCSD at La Jolla Marriott, La Jolla. Fri-Sun. 18 hrs. $175. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

August 28-31—**Current Concepts in Primary Care Cardiology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Mon-Thurs. 18 hrs. $385. Contact: UCD.

September 9—**Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Mariott, Mission Valley, San Diego. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

September 22-23—**Musculoskeletal Problems in Primary Care**. UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sat. 12.5 hrs. Contact: UCSF

September 28-30—**Palliative Medicine Curriculum Development for Physicians in Training.** UCSD at San Diego Hospice. Thurs-Sat. 12 hrs. $275. Contact: UCSD.

September 30—**Clinical Neurology Update for the Primary Care Physician: 1995 Santa Barbara Symposium.** Neurology Education Consortium of Santa Barbara at Radisson Hotel, Santa Barbara. Sat. 7 hrs. $125. Contact: NECSB, P O Box 30020, Santa Barbara 93130. (805) 564-8600.

October 11-13—**10th Annual Primary Care Medicine: Principles and Practice.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 20 hrs. $495. Contact: UCSF.

October 14— **Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Radisson Hotel, Sacramento. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

October 16-18—**Neurology and Outpatient Psychiatry for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 25-28—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

October 26-29—**Nevada Academy of Family Physicians.** NAFP at Tropicana Hotel, Las Vegas, Nevada. Thurs-Sun. 21 hrs. Contact: Barbara Bollin, NAFP, P O Box 27713, Las Vegas, NV, 89126-1713. (702) 647-0117.

November 6-8—**Geriatrics Update 1995**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

December 7-9—**Clinical Care of the AIDS Patient**. UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 24 hrs. $395. Contact: UCSF.

INFECTIOUS DISEASE

November 3-5—**Advances in Infectious Disease**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

August 20-25—**Advances in Internal Medicine**. UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $475. Contact: UCD.

September 29-October 1—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 16.5 hrs. $430. Contact: UCSF.

MANAGED CARE

October 5-7—**Doctors in Distress II.** American College of Legal Medicine at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 17.25 hrs. Contact: ACLM, 611 E Wells St, Milwaukee, WI 53202. (414) 276-1881.

NEPHROLOGY

September 16—**35th Annual Scientific Symposium on Kidney Disease**. National Kidney Foundation of Southern California at Sheraton Universal City. Sat. 6.5 hrs. Contact: Johanna Goldberg, (310) 641-8152.

November 9-10—**International Symposium on Continuous Renal Replacement Therapy.** UCSD. Thurs-Fri. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

September 22-24—**HIV, AIDS and Women**. UCSD at La Jolla Marriott. Fri-Sun. 18 hrs. $175. Contact: UCSD.

October 15—**OB/GYN Pathology**. USC at Red Lion Hotel, Glendale. Sun. 6 hrs. $175. Contact: USC.

October 16-20—**OB/GYN Review**. USC at Red Lion Hotel, Glendale. Mon-Fri. 38 hrs. $640. Contact: USC.

October 23-28—**18th Annual Review Course in Clinical Obstetrics and Gynecology.** Memorial Medical Center/UCI Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Mon-Sat. Contact: MMC/UCI, (310) 933-3811.

December 7-10—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's, Las Vegas. Thurs-Sun. $295. Contact: Center for Continuing Medical Education, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OCCUPATIONAL/ENVIRONMENTAL

October 23-27—**Occupational and Environmental Medicine V**. UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Educaton Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 825-6774.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (213) 342-1544.

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ANAHEIM
ORANGE COUNTY
AAFP-'95

Join your colleagues at the world's largest educational event for primary care physicians!

- Choose from hundreds of CME topics in your favorite learning formats. Evening sessions, too!
- Treat your family to unique education and entertainment, including an evening at Disneyland® Park and another with Mike Love and the California Beach Band.
- Register at Anaheim Convention Center, 800 West Katella, 8:00 a.m.-6:00 p.m. September 20-23. One-day registration on-site, only $100, includes 14 educational features.

Annual Scientific Assembly

September 21-24, 1995 (Additional CME Sept. 20)

American Academy of Family Physicians
8880 Ward Parkway; Kansas City, MO 64114
Questions? Call Assembly Hot Line: 800-926-6890

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OPHTHALMOLOGY

September 16—**Benign Essential Blepharospasm**. UCD at Red Lion Hotel, Sacramento. Sat. 6 hrs. $125. Contact: UCD.

ORTHOPEDICS

November 9-11—**Integrated Function of the Lumbar Spine and Sacroiliac Joints.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 15 hrs. $335. Contact: UCSD.

November 30-December 1—**Disorders of the Upper Extremities.** UCSF at Miyako Hotel, San Francisco. Thurs-Fri. 12 hrs. $375. Contact: UCSF.

OTOLARYNGOLOGY

September 10-15, October 15-20—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 2-4—**San Francisco Otology-Neurotology—1995**. UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 22 hrs. $425. Contact: UCSF.

PATHOLOGY

November 3-5—**45th Annual Meeting of the National Kidney Foundation.** California Convention Center, San Diego. Fri-Sun. 17 hrs. Contact: NKF, 30 E 33rd St, New York, NY 10016. (800) 622-9010.

November 10-11—**Pathophysiology and Treatment of Gastroesophageal Reflux.** USC at at Health Sciences Campus. Fri-Sat. 16 hrs. Contact: USC.

PEDIATRICS

September 22-23—**Ketogenic Diet in the Treatment of Pediatric Epilepsy**. Memorial Medical Center/UCI Center for Health Education at Crowne Plaza Marina Hotel, Redondo Beach. Fri-Sat. Contact: MMC/UCI, (310) 933-3811.

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 19-21—**Practical Pediatric Electrophysiology and Pacing Course.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. Contact: Children's Hospital and Health Center, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 22-26—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital and Health Center at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. Contact: Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 26-28—**34th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15hrs. $295. Contact: David Steward, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

PLASTIC SURGERY

September 9—**17th Annual Symposium.** Los Angeles Society of Plastic Surgeons at Ma Maison Sofitel, Los Angeles. Sat. 6 hrs. $125. Contact: LASPS, 2001 Santa Monica Blvd, Ste 1180W, Santa Monica 90404. (310) 539-6500.

November 4-5—**Endoscopic Plastic Surgery and Beyond**. UCSD. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

November 11-14—**Surgical Advances in Cleft and Cleft Palate.** UCD at Monterey Plaza. Sat-Tues. 18 hrs. $450. Contact: UCD.

December 8-9—**2nd Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources. Fri-Sat. Contact: Martin Borsanyi, c/o Professional Image, (714) 760-1522.

PSYCHIATRY AND NEUROLOGY

September 15-16—**1995 Board Review Course for Added Qualifications in Geriatric Psychiatry.** UCLA and the American Association for Geriatric Psychiatry at Loews Santa Monica Beach Hotel. Fri-Sat. 15 hrs. Contact: California Geriatric Education Center, 10833 Le Conte Ave, 32-144 CHS, Los Angeles 90095-1687. (310) 312-0531.

September 29-October 1—**West Coast Geriatric Psychiatry Conference.** UCSD at Hotel del Coronado. Fri-Sun. 17 hrs. $325. Contact: UCSD.

November 3-5—**41st Annual Group Therapy Symposium**. UCSF. Fri-Sun. Contact: UCSF.

PULMONARY/CRITICAL CARE

October 19-21—**14th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 17 hrs. $430. Contact: UCSF.

September 15-17—**3rd International Symposium on the Difficult Airway**. Memorial Medical Center/UCI Center for Heatlh Education at Sutton Place Hotel, Newport Beach. Fri-Sun. Contact: MMC/UCI, (310) 933-3811.

RADIOLOGY

September 30-October 1—**7th Annual Ultrasound Update 1995.** UCD at Red Lion Hotel, Sacramento. Sat-Sun. 10 hrs. $235. Contact: UCD.

October 21-22—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. 13 hrs. $375. Contact: UCSD.

October 22-23—**Neuroradiology Update**. UCSD at Sheraton Grande Torrey Pines, La Jolla. Sun-Mon. 13 hrs. $375. Contact: UCSD.

October 23-27—**20th Annual San Diego Postgraduate Radiology Course**. UCSD at Hotel del Coronado. Mon-Fri. 27 hrs. $575. Contact: UCSD.

October 27-28—**15th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado. Fri-Sat. 14 hrs. $375. Contact: UCSD.

January 28-February 4—**Multispecialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest Ultrasound and Bone.** UCSD at Hotel del Coronado, San Diego. 1 wk. 40 hrs. Contact: UCSD.

SURGERY

December 1-3—**International Symposium on TMJ Arthroscopy and Arthroscopic Surgery**. Fri-Sun. $695. Contact: Peg Hoelderlin, c/o Professional Image, (714) 760-1522.

GENERAL/MULTIDISCIPLINARY

August 28-September 1—**Medical Informatics Introductory Short Course**. Stanford University's Center for Advanced Medical Informatics at Stanford. Mon-Fri. 34.25 hrs. $900-$1300. Contact: Irene Zagazeta, (415) 723-6979.

September 14-15—**4th Regional Symposium on the Design and Methods of Clinical Trials**. UCSF at San Francisco. Thurs-Fri. 12.5 hrs. $350. Contact: UCSF

September 30—**Outcomes: More Than a Buzzword—A Symposium on Outcomes Studies for Health Care Professionals**. FHP Healthcare at Anaheim Hilton and Towers. Sat. 6 hrs. $65. Contact: Tina Pirzadeh, (714) 378-5780..

October 7—**Multi-Cultural Diversity in Health Care Symposium**. UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

December 23-29—**Advances in Medicine 1995.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Fri. 6 hrs. $475. Contact: Symposium Maui, PO Box 10185, Lahaina, HI 96761. (808) 661-8032.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

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Brochures, course information, and registration forms are available from the contact person or organization.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

August-November—**Level II Reaccreditation Seminars**. Colorado Department of Labor and Employment, Division of Workers' Compensation, in Denver, Grand Junction, and Colorado Springs. Contact: Faye Boyd, Accreditation Coordinator, Dept of Labor, (303) 575-8756.

September 8-9—**Alzheimer's Disease Update for Physicians.** University of Colorado Health Sciences Center at Red Lion Inn, Denver. Fri-Sat. Contact: U of Colo.

September 28-29—**Informatics Fair '95: Computers in Medicine.** Denver Medical Library at Presbyterian/ St Luke's Hospital. Contact: Denver Medical Library, (303) 839-6670.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Medical Education, Primary Children's Medical Center, Salt Lake City, at Sun Valley Resort, Sun Valley. Fri-Sun. Contact: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City, UT 84113. (80l) 588-2000.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

.October 7-8—**Pediatrics for the Practitioner—Back to the Basics**. New Mexico Pediatric Society at the Roswell Inn, Roswell. Sat-Sun. Contact: Steve Yabek, MD, NM Pediatric Society, 715 Grand Ave NE, Ste 207, Albuquerque 98102. (505) 848-3700.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

October 27-28—**ECG, Interpretation for the Primary Care Physician**. New Mexico Heart Institute at the Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, NM Heart Institute, 1001 Coal SE, Albuquerque 87106. (505) 841-1001 or (800) 888-6642.

November 17-18—Parkinson's Disease and Movement Disorders for the Practitioner. Mayo Clinic Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic Scottsdale, 13400 E Shea Blvd, Scottsdale 85259. Phone, (602) 301-7447; fax (602) 301-8323.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Contact: Billie Dytzel, (505) 265-0732.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Education at Sun Valley Resort, Sun Valley, Idaho. Fri-Sun. Contact: PCMC.

October 27-29—**Intensive Interactive Head and Neck Imaging Course**. University of Utah at Marriott Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Contact: UUMS.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

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OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 22-25—**Trauma Radiology: 1995**. Seattle. Tues-Fri. Contact: IMM, (713) 965-0566.

August 25-26—**Laparoscopic Surgery of Colon and Appendix**. Seattle. Fri-Sat. Contact: U/W.

September 9-13—**Intensive Training Workshop in Dialectical Behavior Therapy**. Seattle. Sat-Wed. Contact: U/W, (206) 543-9886.

September 11-15—**23rd Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 14-16—**Symposium on Teaching Internal Medicine**. Seattle. Thurs-Sat. Contact: U/W.

September 15—**Understanding Radioactive Waste and Public Health Concerns.** Seattle. Sat. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

September 22-23—**Laparoscopic Surgery: Upper GI**. Seattle. Fri-Sat. Contact: U/W.

September 25-29—**Respiratory Protection.** Anchorage. Tues-Sat. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

September 28—**Infectious Disease Conference.** Renton. Thurs. Contact: Valley Medical Center, (206) 575-4721.

September 29-30—**Topics in Internal Medicine**. Seattle. Fri-Sat. Contact: VMMC.

September 29-30—**Breast Cancer Update.** Seattle. Fri-Sat. Contact: U/W.

October 5-6—**ACLS**. Seattle. Thurs-Fri. Contact: VMMC.

October 6—**John Locke Cardiology.** Seattle. Fri. Contact: Swedish, (206) 386-2265.

October 6—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

October 6-7—**Musculoskeletal Diseases for the Primary Care Physician**. Seattle. Fri-Sat. Contact: U/W.

October 11—**Complex Chemical Exposures: Soft Data, Hard Issues.** Portland. Wed. Contact: Center for Occupational Health and Safety, (206) 543-1069.

October 21—**Practical Pediatrics.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

October 21-22—**ACLS**. Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

October 25—**The Changing Workplace: Effective Measures to Cope With Job Stress.** Seattle. Wed. Contact: Center for Occupational Health and Safety, (206) 543-1069.

October 26-27—**Current Concepts in Drug Therapy**. Seattle. Thurs-Fri. Contact: U/W.

October 27—**7th Annual Current Concepts in Perinatology**. Tacoma. Fri. Contact: Multicare, (206) 552-1221.

October 27-28—**Mental Health Update: Training in...**Seattle. Fri-Sat. Contact: U/W.

November 2-3—**Ergonomics of Occupational Hand-Arm and Whole-Body Vibration.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 3—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

November 10-11—**6th Annual Regional Conference for Occupational Therapy and Physical Therapy.** Seattle. Fri-Sat. Contact: U/W.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

Novembr 13—**New Ways of Organizing Data: Geographical Information Systems.** Seattle. Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 16-18—**Surgery Update**. Seattle. Thurs-Sat. Contact: U/W.

November 17—**Pinkham Basic Science Lectureship**. Seattle. Fri. Contact: Swedish, (206) 386-2265.

November 24—**Urology Update.** Seattle. Fri. Contact: VMMC.

November 30—Air Pollution: Has Particulate Matter Increased Mortality? Lessons From Seattle and Spokane. Seattle. Thurs. Contact Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 1—**Pediatrics Update**. Seattle. Fri. Contact: VMMC.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9—**Fiberoptic Intubation**. Seattle. Sat. Contact: U/W.

December 14—**Clinical Recognition of Health Hazards in the Home.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety.

December 14-16—**Primary Care for the Ob/Gyn**. Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference.** Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

January 11-12—Ergonomics. Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 20—Pharmacology Update. Seattle. Sat. Contact: Swedish Hospital, (206) 386-2265.

January 25—**Ethical Issues in Occupational Health**. Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

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Articles

Sea-Level Physical Activity and Acute Mountain Sickness at Moderate Altitude

BENJAMIN HONIGMAN, MD, *Denver, Colorado*; MARTIN READ, MD, *Seattle, Washington*; DENNY LEZOTTE, PhD, *Denver, Colorado*; *and* ROBERT C. ROACH, PhD, *Albuquerque, New Mexico*

The effect of previous physical conditioning on young well-conditioned mountaineers in relationship to acquiring acute mountain sickness is controversial. Data show both increased and decreased effects on the incidence of altitude illness. How general tourists at moderate altitudes are affected is unknown. To determine the influence of sea-level habitual physical activity on the incidence of mountain sickness, we surveyed 205 participants in a scientific conference at 3,000 m (9,840 ft). A 36-item questionnaire was distributed to the subjects 48 hours after arrival at altitude. Their sea-level physical activity (SLPA) was measured by a published and validated instrument that included questions about patterns of work, sporting, and leisure-time activities. Acute mountain sickness was defined as the presence of 3 or more of the following symptoms: headache, dyspnea, anorexia, fatigue, insomnia, dizziness, or vomiting. Most of the respondents were male (62%) from sea level (89%) with a mean age of 36 ± 8.7 (standard deviation) years (range, 22 to 65). Nearly all (94%) were nonsmokers, and 28% had acute mountain sickness. The mean SLPA score was 8.0 ± 1.3 (range, 5.1 to 12.0). No statistically significant difference in mean SLPA scores was found between those with and without acute mountain sickness (8.1 versus 7.8), nor in the individual indices (work, 2.5 versus 2.4; sport, 2.9 versus 2.7; leisure, 2.8 versus 2.7). We conclude that habitual physical activity performed at sea level does not play a role in the development of altitude illness at moderate altitude in a general tourist group.

(Honigman B, Read M, Lezotte D, Roach RC: Sea-level physical activity and acute mountain sickness at moderate altitude. West J Med 1995; 163:117-121)

Acute mountain sickness (AMS) is a symptom complex consisting of headache, dizziness, insomnia, and gastrointestinal complaints that occurs in 12% to 60% of travelers to altitude.[1,2] Although most studies concerning AMS and other related altitude illnesses have been conducted on small physically fit groups with exposure to very high altitudes, millions travel to moderate elevations, and AMS may develop in as many as 25%.[3,4]

The rapidity of ascent, the elevation attained, and underlying pulmonary problems have been identified as increasing the risk of symptoms developing.[1,3] The effect of physical conditioning on the development of AMS, however, remains unknown. Studies conclude that greater levels of aerobic capacity increase[5] or have no effect on the risk of AMS developing.[6,7] Others suggest that physically fit persons are better able to tolerate mild to moderate symptoms.[8]

We, therefore, studied a group of tourists traveling to moderate altitude to determine the association of sea-level habitual physical activity (SLPA) with the development of AMS and to determine whether SLPA can be used to predict persons at risk for altitude illness.

Subjects and Methods

The study group consisted of 205 adults attending a scientific conference at a Rocky Mountain resort located at 3,000 m (9,840 ft). Most (128 [62%]) participants were male; their mean age was 36 ± 8.7 years (standard deviation) (range, 22 to 65); 182 (89%) lived at sea level (below 1,000 m [3,280 ft]); 194 (94%) were nonsmokers; and 125 (61%) had at least one alcoholic drink after arrival. The mean body-mass index[9]—weight in kilograms ÷ height in m^2—demonstrated that the study group was representative of the general population in terms of body habitus (male = 23.7 ± 4.5; female = 21.1 ± 5.1).

The conference was chosen as one whose schedule required all participants to attend an early morning meeting within 48 hours of arrival, when the questionnaire could be distributed. Study personnel attended this meeting and distributed and collected the questionnaire as participants

From the Division of Emergency Medicine, Department of Surgery (Dr Honigman), and the Department of Preventive Medicine and Biometrics (Dr Lezotte), University of Colorado Health Sciences Center, Denver; the Colorado Altitude Research Institute, Keystone, Colorado (Drs Honigman and Roach); Virginia Mason Hospital, Seattle, Washington (Dr Read); and the Department of Cardiopulmonary Physiology, The Lovelace Institutes, Albuquerque, New Mexico (Dr Roach).

This is one of several projects developed at the Colorado Altitude Research Institute, Keystone, Colorado. Funding for the project was from a National Institutes of Health summer short-term training grant at the University of Colorado School of Medicine.

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ABBREVIATIONS USED IN TEXT

AMS = acute mountain sickness
SD = standard deviation
SLPA = sea-level [habitual] physical activity
Vo_2max = maximum oxygen consumption

passed through the one available doorway. The survey instrument was completed by 96% of the persons attending the meeting, and data satisfactory for analysis were obtained in 99% of completed surveys.

Questionnaire

The questionnaire was designed to elicit data regarding demographics, level of habitual physical activity, and symptoms of AMS.

Sea-level physical activity was measured using an instrument developed by Baecke and co-workers.[10] It is a compilation of constituent indices measuring activity at work, during sports, and during leisure time. Responses were assessed on a 5-point Likert scale—never, seldom, sometimes, often, always—except for two that asked for type of activity. The first was occupation, which was then coded into one of the three levels as defined by The Netherlands Nutrition Council.[11] Low-level work activity corresponded to clerical work, shopkeeping, teaching, and medical practice; middle-level activity corresponded to factory work and farming; and high levels of work activity included jobs such as construction work and professional sports. These are similar to occupational and physical activity classifications developed by other investigators.[12,13] In addition to job class, calculations of work activity included questions regarding the amount of time spent sitting, standing, walking, and lifting heavy loads and the amount of fatigue at the end of a workday.

Sports activity was compiled from questions concerning the type of sport and frequency, duration, and exertion while playing. Types of sports were divided into three categories.[13] The lowest category, represented by sports such as sailing and bowling, corresponded to an average energy expenditure of 0.76 megajoules (MJ) per hour. The middle level corresponded to 1.26 MJ per hour and included tennis and swimming. The highest level included rowing and basketball and represented an average expenditure of 1.76 MJ per hour.

Leisure-time activity was distinguished from sports activity by asking questions regarding the amount of time spent watching television, walking, and cycling in absolute terms and in reference to others of the same age.

Acute mountain sickness was defined as the presence of three or more of the following symptoms after recent exposure to altitude: loss of appetite, vomiting, shortness of breath, dizziness or lightheadedness, unusual fatigue, insomnia, or headache. This definition is similar to that used by other investigators.[1,3,4,14-16] Participants were asked to respond yes or no to a question asking them if they had experienced any of the above symptoms since arriving at the resort.

Statistical Analysis

Participants were classified as having or not having AMS, and then demographic and activity variables were compared using the Student's t test for normally distributed variables and the χ^2 test for discrete variables.

An analysis of variance was used to study the mean SLPA scores between groups of participants with differing numbers of accumulated symptoms. Forward-stepwise multiple logistic regression was used to examine the independent effect of SLPA, adjusting for age and altitude of permanent residence, both of which have previously been shown to be associated with the occurrence of AMS.[2] Sea-level physical activity was evaluated both as a continuous response attribute and a grouped variable; age was always incorporated as a continuous response; permanent residence was dichotomized into sea level (below 1,000 m) and above sea level. All calculations were performed using the SAS statistical software package. Variations are expressed as standard deviations. Associations were considered significant if they achieved a probability level of less than .05.

Results

Of the study group, 28% reported having three or more symptoms and hence met the case definition for AMS. At least one symptom was reported by 73%, with headache being the most common (n = 120 [59%]). Insomnia (58 [28%]) and unusual fatigue (48 [23%]) were present in many visitors, but dizziness (35 [17%]), anorexia (28 [14%]), and vomiting (5 [2%]) were seen less commonly.

The distribution of SLPA scores is shown in Figure 1. The mean SLPA score was 8.0 ± 1.3, with values normally distributed around the mean according to goodness-of-fit tests. The individual components of SLPA scoring were as follows: mean work activity, 2.4 ± 0.3; mean sport activity, 2.8 ± 0.8; and mean leisure activity, 2.8 ± 0.6.

When SLPA scores were compared between those with and without AMS, no significant differences were found (Table 1). Mean SLPA scores for the two groups were 7.8 ± 1.3 and 8.1 ± 1.2, respectively. Similarly, no differences were found between the two groups when the constituent indices of SLPA were compared. Of note, however, is that the leisure-time index (time spent watching television, reading, and so forth) tended toward significance ($P = .06$).

To further investigate the association of SLPA with an increased number of symptoms defining AMS, a one-way analysis of variance was used. Figure 2 plots the mean SLPA scores stratified by the number of AMS symptoms. This analysis failed to demonstrate differences in the mean SLPA scores between these groups ($P = .64$, $R^2 = .01$).

Forward-stepwise multiple logistic regression also failed to show that SLPA, after adjusting for age and sea-level residence, was predictive of AMS developing ($P = .16$).

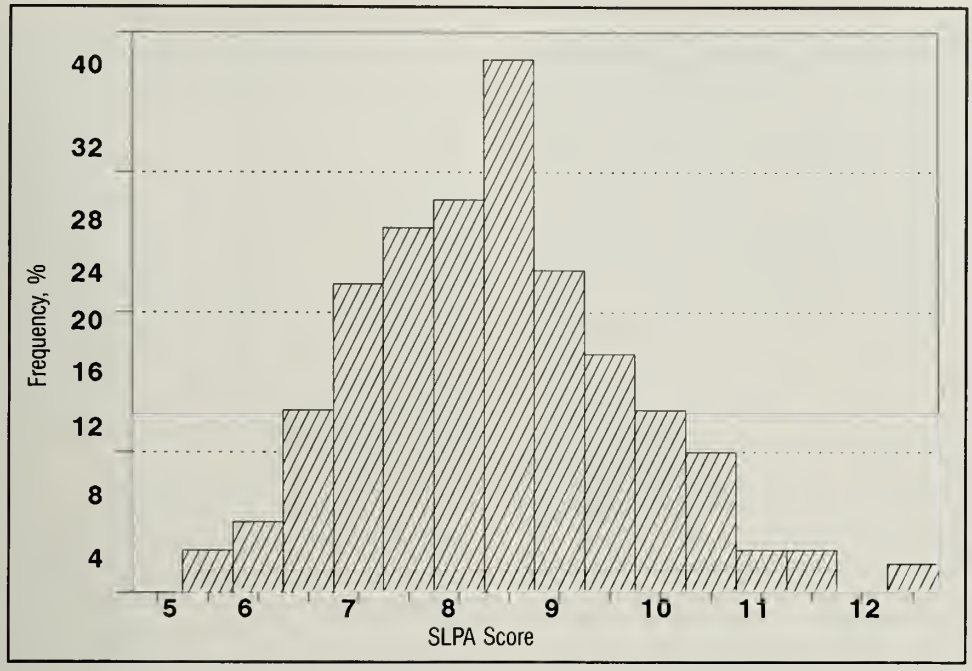

Figure 1.—The graph shows the distribution of sea-level physical activity (SLPA) scores in visitors to moderate altitudes.

Discussion

The main finding of this study is that there was no apparent association between sea-level habitual physical activity and the development of acute mountain sickness in the general population traveling to moderate altitude (3,000 m). This report represents the largest observation of persons who have a broad range of activity patterns at sea level and the influence of these fitness levels on altitude illness.

Despite Ravenhill's early observation that "young, strong and healthy men may be completely overcome [by AMS] while stout plethoric individuals . . . may not even have a headache,"[17(p315)] the precise effect of physical fitness on the development of AMS remains unknown.

In two studies, hundreds of persons in the Indian army who traveled to between 3,000 and 4,500 m (9,840 and 14,760 ft) were studied, and the investigators noted that AMS developed in all types of persons "without any

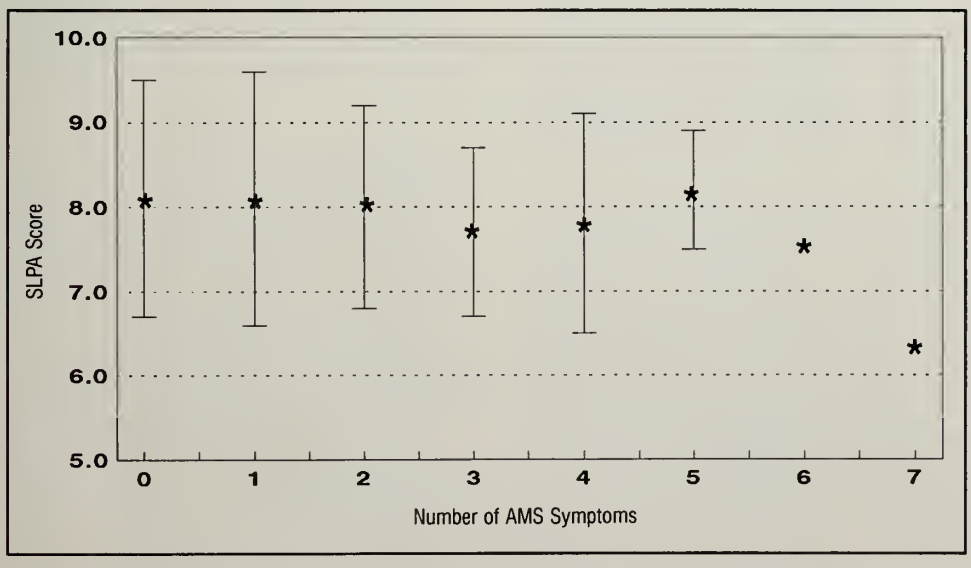

Figure 2.—The graph shows the distribution of mean sea-level physical activity (SLPA) scores by the number of symptoms of acute mountain sickness (AMS) in visitors to moderate altitudes. The asterisks (*) signify the means and the vertical lines the ranges (distribution).

TABLE 1.—*Mean Sea-Level Habitual Physical Activity (SLPA) Scores in Those Visitors With and Without Acute Mountain Sickness (AMS) at Moderate Altitudes*

SLPA Score	AMS	Non-AMS	P Value
Overall score	7.8	8.1	.15
Constituent scores			
Work	2.5	2.4	.09
Sport	2.7	2.9	.09
Leisure	2.7	2.8	.06

predilection for the obese."[2,18] No information other than weight was used to measure fitness. Previous work in a tourist population[3] and in a group of Japanese trekkers,[19] however, showed that persons who were obese had a higher incidence of AMS. Rennie has stated that AMS is not "in any way related to the state of physical training,"[6] whereas Hackett has observed that

> fit persons are better able to tolerate mild and moderate AMS. Persons struggling into camp each day because of their poor conditioning will often find even mild AMS unbearable . . . whereas more fit individuals might 'tough it out.'[8p137]

Yet, the direct effect of physical fitness has been only minimally studied, using maximum oxygen consumption (Vo_2max) on the development of AMS,[5,7] and these results are conflicting. In one of the studies, no correlation was found between predeparture Vo_2max values and the incidence of AMS in 17 marines at 4,500 m, but few of these persons had AMS because they took seven days to reach their destination.[7] A second study showed, however, that the levels of aerobic fitness as measured by the Vo_2max did affect the severity of AMS in 12 young men at 4,300 m (14,110).[5] Although both of these studies used a physiologic measure of fitness, they were limited to small groups of healthy young men.

Our report supports the results of others.[1,7] Because of the size of the group studied, we were unable to use precise markers of cardiorespiratory fitness such as the Vo_2max. We, therefore, measured fitness by using a detailed questionnaire specifically developed to study habitual activity levels as a measure of physical fitness in the general population.

Several authors have addressed the assessment of physical activity in epidemiologic studies and its relationship with physical fitness.[20-23] A consensus statement developed at the 1988 Toronto Conference on Exercise, Fitness, and Health stated that habitual physical activity influences fitness despite individual health status differences.[24] The National Heart, Lung, and Blood Institute found that survey methods using physical activity indices are associated with ten-year coronary heart disease rates. The indices are more sensitive in persons with high levels of physical activity than in sedentary persons.[25] A significant and positive correlation was found between treadmill performance and leisure-time physical activity and leisure-time physical activity and personal reports of sweating and dyspnea.[26] Finally, an investigator found that leisure-time physical activity correlated well with submaximal physical work capacity.[27] Although the questionnaire we used has not previously been used for altitude investigations, it has been shown to be valid, has good test-retest reliability, is nonreactive, and is easy and quick to have participants complete without help from interviewers. There are several other general surveys available for assessing physical activity,[28,29] as well as several quantitative history surveys,[30,31] recall surveys,[32,33] and diary methods.[34] Many of these instruments have been developed to study the effects of physical activity on heart disease, and they often focus on one aspect of physical activity, for example, leisure- or job-related activity. Because most of these require substantial amounts of time to complete, are focused on only one area of activity, or require a trained interviewer to administer, they were not selected for our study.

Although our results suggest that active persons are no more at risk for the development of AMS than those who are less fit, the number of persons in this active group was small. In addition, it is possible that the questionnaire is not sensitive to the extremely fit or elite athlete, therefore possibly invalidating our results in this group. A further limitation of the instrument is that no questions were asked regarding the specific activity undertaken at altitude. It may be that some persons may be more active at altitude, thus increasing the risk of AMS developing. Despite these limitations, we think the results can be applied to the general population of travelers visiting moderate altitudes.

Our findings that sea-level habitual physical activity is not associated with AMS and is not predictive of who will have mountain illness supports the fact that no one is immune from this disorder. This may help practicing clinicians when advising their patients regarding travel to moderate altitudes.

Acknowledgment

Charles S. Houston, MD, provided direction and support, Jules Lichtig assisted with the data collection, and Steven R. Lowenstein, MD, and Jane Koziol-McLain assisted with the data analysis.

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Articles

Argon and YAG Laser Photocoagulation and Excision of Hemangiomas and Vascular Malformations of the Nose

DAVID B. APFELBERG, MD, *Atherton, California*

A total of 22 patients—19 children, 3 adults—with a variety of hemangiomas and vascular malformations of the nose were treated over a 5-year period. Various laser modalities were used. Some lesions could be photocoagulated by the argon or the yttrium-aluminum-garnet (YAG) laser. Larger lesions were resected with the YAG laser and sapphire tips. Preliminary arteriography with superselective embolization was necessary in 1 patient. Total removal was possible in 13 patients, and no complications or side effects were noted.

(Apfelberg DB: Argon and YAG laser photocoagulation and excision of hemangiomas and vascular malformations of the nose. West J Med 1995; 163:122-127)

Nasal hemangiomas present surgeons with a difficult therapeutic dilemma. Although many will involute spontaneously, others will not. Their rapid growth may be alarming and deforming, with distortion of adjacent nasal structures (nostrils, alar cartilage) that can have long-term residual effects. In addition, the obvious visible deformity in the center of a child's face presents a severe emotional burden initially for the parents and secondarily for the child as peer curiosity and ridicule are directed toward the deformity. Satisfactory reconstructive and cosmetic results have been achieved in a series of 22 patients treated for various nasal vascular lesions with the yttrium-aluminum-garnet (YAG) or argon laser.

Patients and Treatment

Over a five-year period between 1988 and 1993, 22 patients—15 female, 7 male—were treated. There were 3 adults aged 19, 24, and 34 and 19 children aged 6 months to 10 years (average, 26.6 months). The diagnosis was either capillary hemangioma or venous malformation in 16 patients, vascular malformation in 5 patients, and arteriovenous malformation in 1 patient. Six lesions were located on the tip of the nose, 15 on the dorsum, and 1 at the base of the nostril. Complete shrinkage or removal was achieved in 16 patients, and in 6 patients, treatment resulted in subtotal removal or shrinkage. Early in the series, 3 patients underwent argon laser photocoagulation (Figures 1 and 2). Argon laser photocoagulation is not usually used, with the more modern tunable dye laser being favored for photocoagulation. Five patients underwent YAG laser photocoagulation plus the intralesional administration of steroids (Figure 3), followed by YAG laser resection in 3 patients. A total of 16 patients had YAG laser resection (Figures 4, 5, and 6), and 1 patient had previous superselective embolization.

Discussion

The natural history of vascular abnormalities of the head and neck has been well described. The current classification divides the lesions into two main categories.[1,2] Vascular malformations may or may not be present at birth, but continue to grow during life, with occasional growth spurts at certain times. They contain mature-appearing, orderly, nonproliferative endothelial cells lining the vascular spaces with a relatively low number of mast cells. Hemangiomas are usually not present at birth, contain less orderly, immature, proliferating endothelial cells, and a relatively high number of mast cells. These lesions progress and enlarge rapidly and may then involute totally or subtotally.

Nasal vascular lesions present a particularly difficult dilemma. Although many may be hemangiomas, which means that they may eventually involute, their growth and subsequent deformity with the distortion of delicate nasal architecture often demand treatment. Similarly, subtotal involution still leaves a visible deformity. True vascular malformations do not involute, and their subsequent hypertrophy makes resection more difficult in the future. Regardless of the natural course, children and their parents must suffer the emotional distress of a visible facial deformity in the center of the face. Thus, debate has focused on surgical versus nonsurgical treatment of these disorders. All patients' families must be advised about the natural course of spontaneous involution before any intervention is attempted. Such regression may be delayed as long as 8 to 11 years and in some lesions may never occur.

From the Atherton Plastic Surgery Center, Atherton, California.
Reprint requests to David B. Apfelberg, MD, Atherton Plastic Surgery Center, 3351 El Camino Real, Ste 201, Atherton, CA 94027.

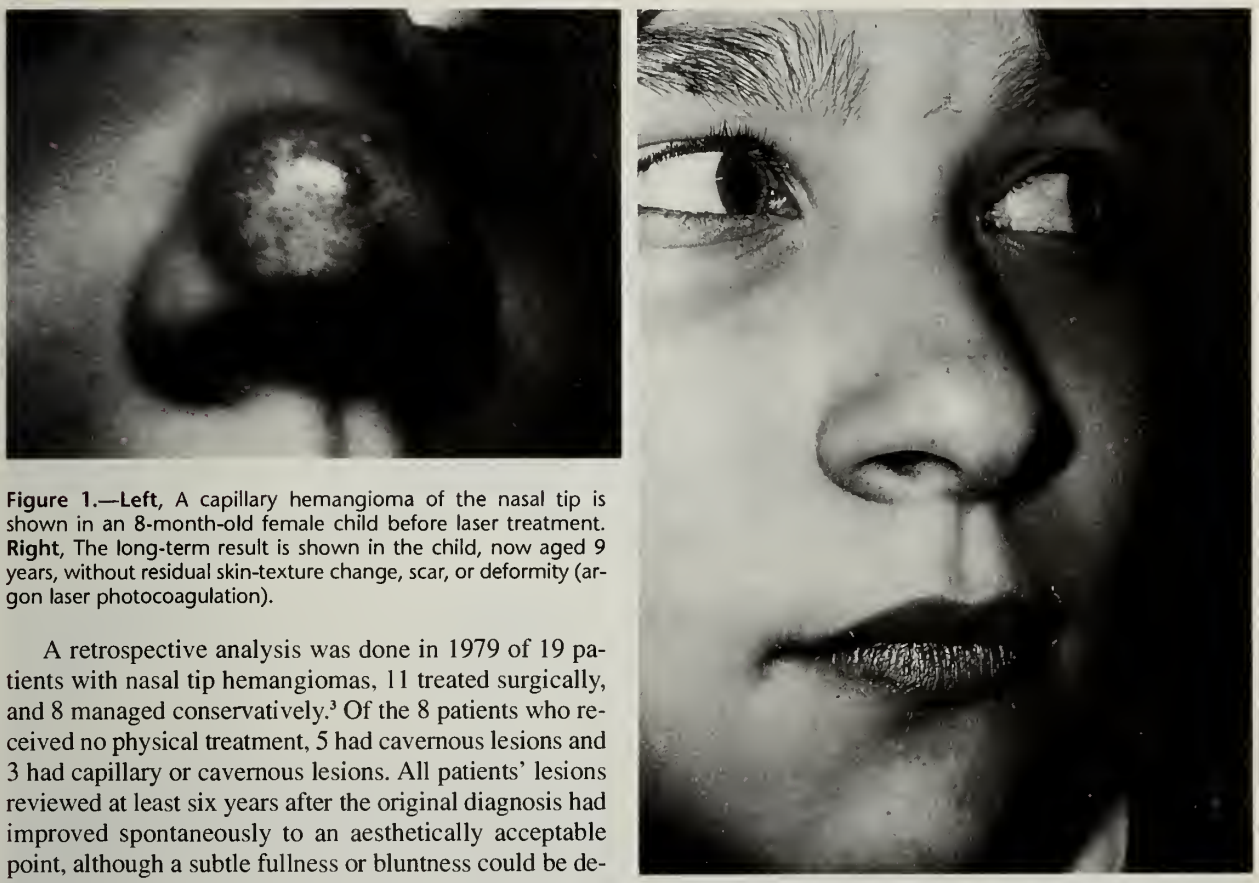

Figure 1.—Left, A capillary hemangioma of the nasal tip is shown in an 8-month-old female child before laser treatment. **Right,** The long-term result is shown in the child, now aged 9 years, without residual skin-texture change, scar, or deformity (argon laser photocoagulation).

A retrospective analysis was done in 1979 of 19 patients with nasal tip hemangiomas, 11 treated surgically, and 8 managed conservatively.[3] Of the 8 patients who received no physical treatment, 5 had cavernous lesions and 3 had capillary or cavernous lesions. All patients' lesions reviewed at least six years after the original diagnosis had improved spontaneously to an aesthetically acceptable point, although a subtle fullness or bluntness could be detected in each nose. Of the 11 patients who were treated surgically, 10 had capillary or cavernous lesions and 1 had a cavernous lesion. Each patient had an average of four procedures, with half the surgical procedures being followed by delayed wound healing. In 8 patients, the surgical result was an improvement over the original condition, but in only 3 was it considered "aesthetically acceptable." In three other patients the results were neither surgically nor aesthetically acceptable. The authors' conclusion was to recommend "no touch" management of hemangiomas of the nasal tip. They did not discuss nasal hemangiomas in other locations on the nose. The series being reported comprised 6 patients with hemangiomas of the nasal tip and 16 patients with lesions in other locations on the nose. Also, surgical techniques have progressed greatly since 1978, and several operations (average of 4 per patient) with 50% delayed wound healing would be considered excessive today.

Good results were described following the resection of nasal tip hemangiomas with the use of a noncrushing clamp as an adjunct for hemostasis.[4] Also, a giant hemangioma of the nasal bones was successfully removed, with a satisfactory cosmetic result.[5]

Serious consideration must be given to indications for laser treatment, either by photocoagulation or resection, versus "watchful waiting." Obstructed nasal airways, bleeding, and severe deformity of the adjacent cartilage or

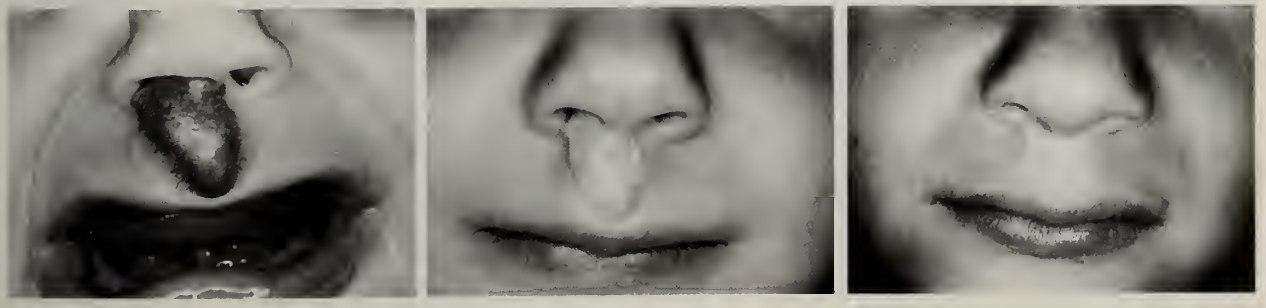

Figure 2.—Left, A capillary hemangioma totally obstructs the nostril and alar base in a 7-month-old child. **Middle,** Shrinkage and blanching were produced 6 weeks after argon laser photocoagulation. **Right,** The long-term result in the child, now aged 6, shows minor residual skin-texture change. (Photographs courtesy of M. R. Maser, MD, Palo Alto, California.)

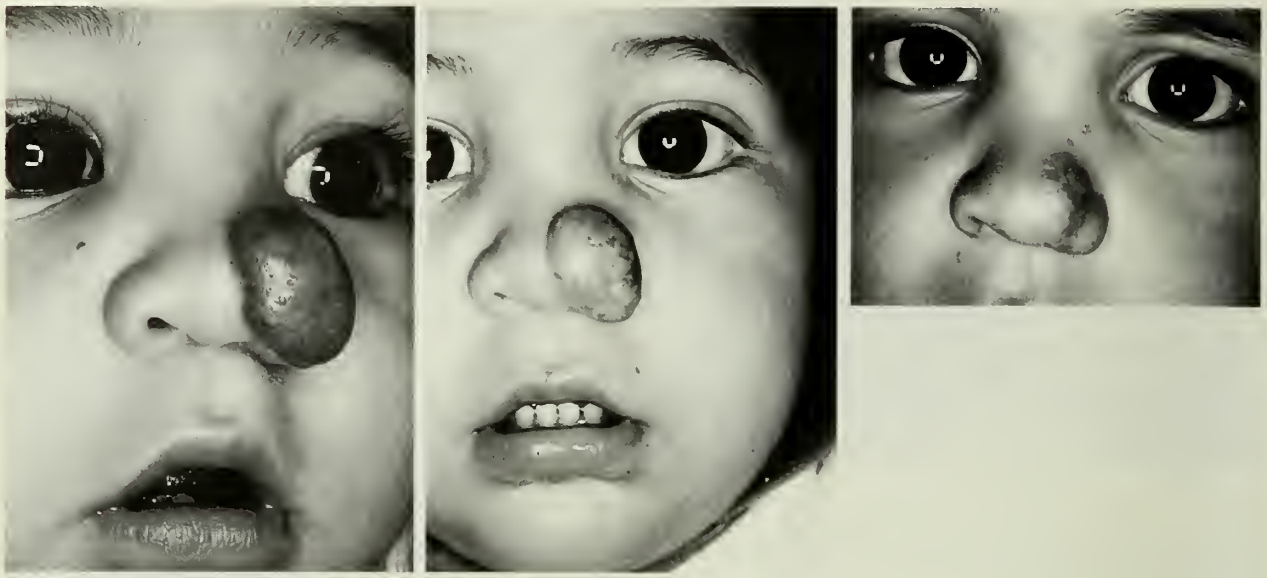

Figure 3.—Left, A rapidly growing capillary or cavernous hemangioma is shown on the left ala in a 16-month-old child. **Middle**, Fibrosis, shrinkage, and blanching are present 4 months after yttrium-aluminum-garnet (YAG) laser photocoagulation plus the administration of intralesional steroids. **Right**, The final result after YAG laser excision with sapphire contact tips shows satisfactory nasal contour, total removal of the hemangioma, and minor residual scarring.

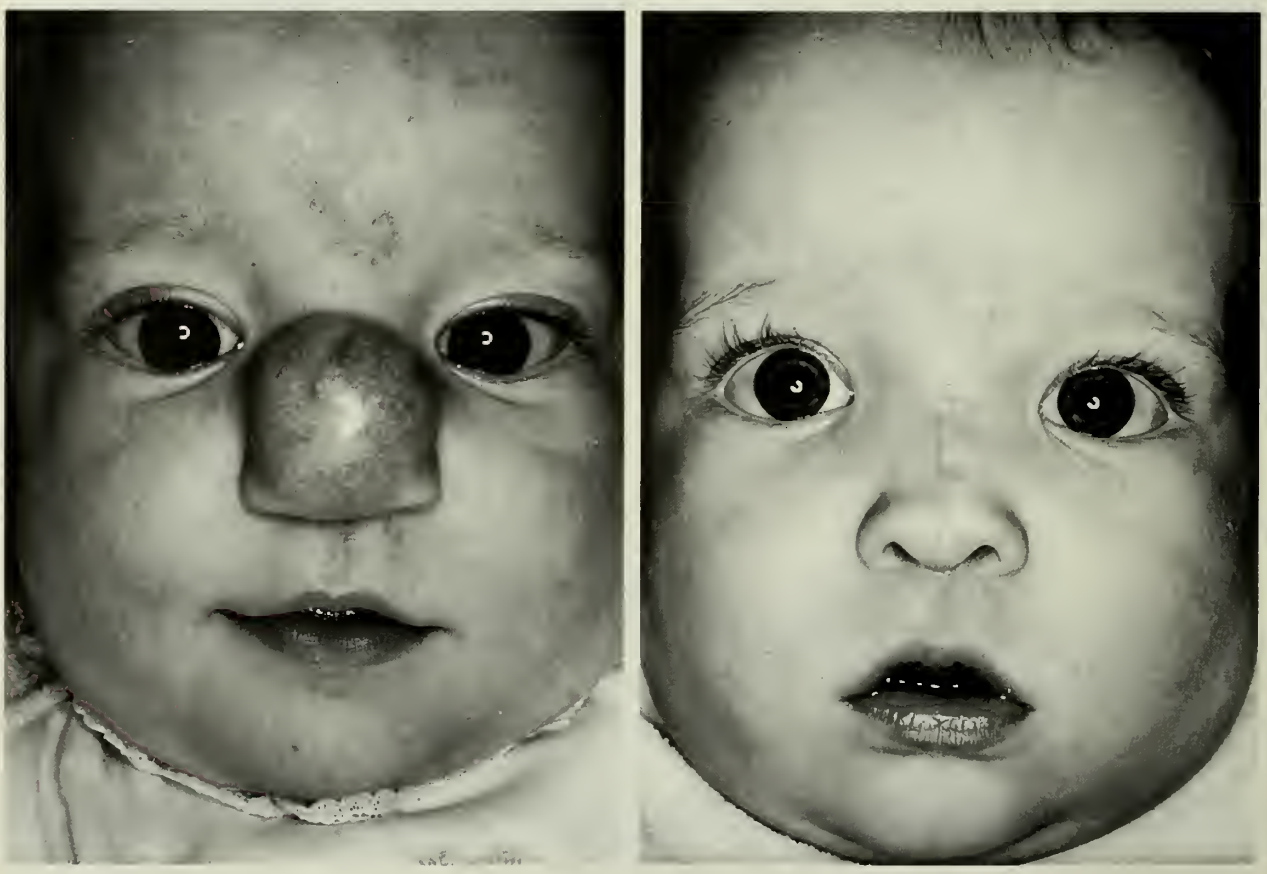

Figure 4.—Left, A capillary or cavernous hemangioma is shown on the nasal dorsum in an 18-month-old female infant. **Right**, The results 6 weeks after yttrium-aluminum-garnet laser resection with contact sapphire-tip laser show total removal of the hemangioma and minor residual scarring.

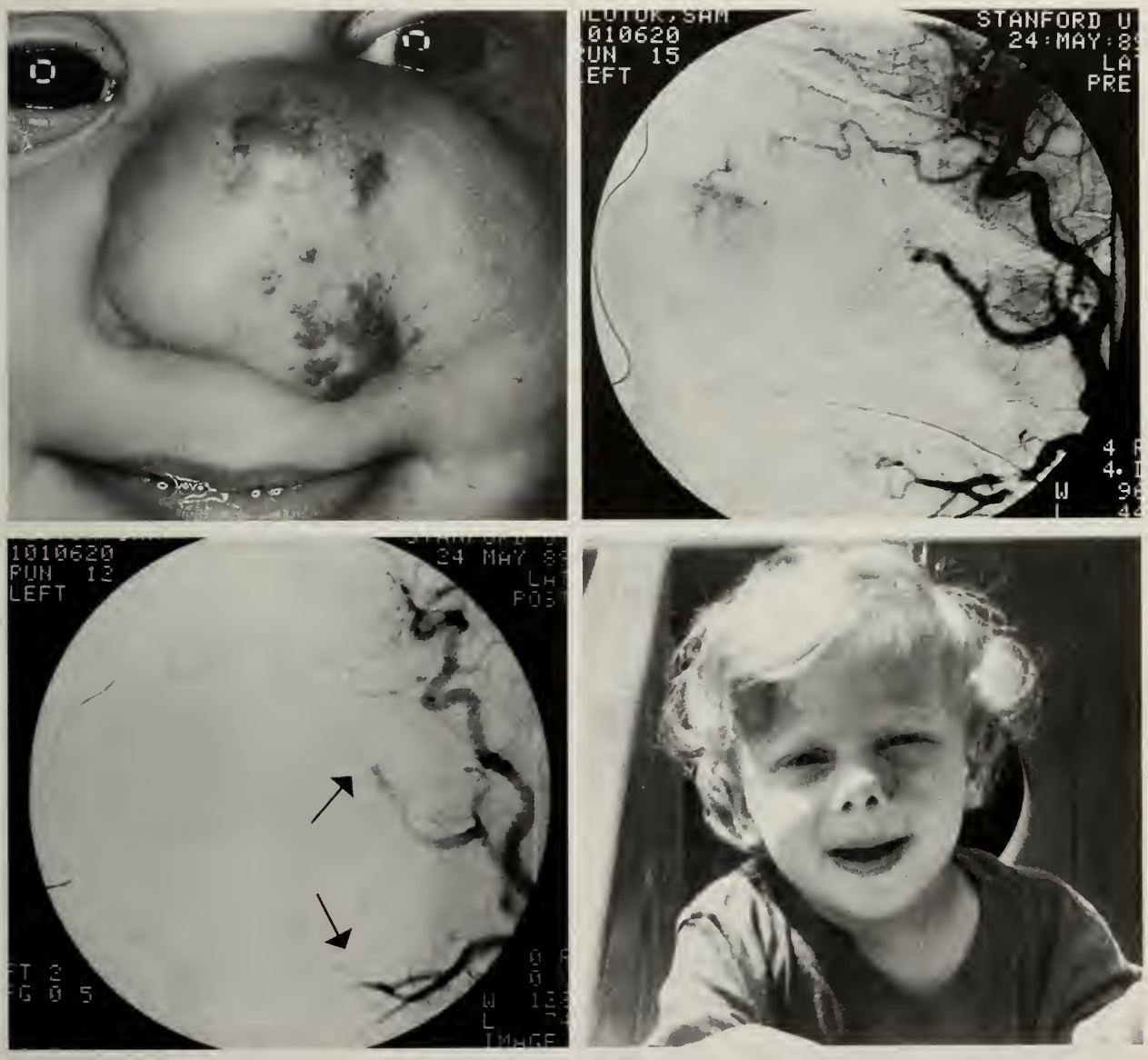

Figure 5.—Top left, A massive, continually growing vascular malformation totally obliterates the nasal architecture in a 13-month-old male infant. **Top right,** A preoperative arteriogram shows an extensive vascular supply from internal maxillary and facial arteries. **Bottom left,** A postembolization arteriogram shows occlusion of the major afferent supply and pronounced decompression of the hemangioma (**arrows**). **Bottom right,** The final appearance is shown 6 months following total resection of the hemangioma with yttrium-aluminum-garnet (YAG) laser contact sapphire tips and 100 ml of blood loss. There was complete removal of the hemangioma with a satisfactory nasal contour and minor residual deformity. (Photographs used with permission of *Plastic and Reconstructive Surgery.*[20(p74)])

nasal bones that lead to growth abnormalities are absolute indications. Parental anxiety and the diagnosis of a vascular malformation (usually noninvoluting) are secondary considerations. Even natural involution may result in a shiny, atrophic redundant skin that is often as or more unsightly than the minor textured change seen after laser photocoagulation. Surgical resection can be planned from a nostril rim or open rhinoplasty approach, thus limiting visible scarring. The timing of intervention is planned when involution is unlikely (no decrease in size has occurred during a 1-year period of observation, or it has continued to enlarge) or when adjacent structures are compromised.

Nonsurgical treatment includes the administration of parenteral or topical steroids, sclerotherapy, pressure, the use of interferon alfa, and irradiation. Irradiation and pressure are probably contraindicated because of possible chronic injury to underlying cartilage and bone, resulting in later growth disturbances. Similarly, the use of interferon alfa is probably not indicated except for massive or life-threatening lesions.[6] Sclerotherapy with agents such as a hypertonic saline solution, sodium tetradecyl sulfate, and the like, may be effective,[7,8] but their use is difficult and painful in the nose. The intralesional administration of steroid may be effective in causing a cessation of growth, blanching of color, and initiation of subsequent

Figure 6.—Left, A capillary hemangioma is shown on the nasal tip in a 9-month-old male infant. **Middle and Right,** A satisfactory result is obtained following yttrium-aluminum-garnet laser resection.

involution.[9,10] A series of injections may be required at intervals of three to four weeks. The use of parenteral steroids in doses of 2 to 4 mg per kg may be indicated for rapidly growing lesions, lesions that are complicated by bleeding or ulceration, or those that obstruct the nasal airway. Few long-term side effects such as growth disturbances, diabetes mellitus, or personality changes have been associated with such treatment.[11,12]

Various lasers can also offer substantial benefit. Early recognition and immediate treatment of the flat, small, red or pink blush that often precedes the development of an obvious hemangioma may prevent any further development. For such treatment, the use of argon and tunable dye lasers has been advocated.[13,14] Their depth of penetration to about 1 mm into the upper dermis limits their usefulness to thin, superficial lesions only, however. The YAG laser penetrates to 4 to 6 mm, thus rendering it more valuable in the photocoagulation of thicker, more hypertrophic lesions. Overlying skin always develops textural changes or scarring to some degree. More well-developed lesions may be fibrosed by photocoagulation with the YAG laser, often in conjunction with the administration of intralesional steroids.[15] Elsewhere my colleagues and I described the use of a frequency-doubled YAG laser to treat a capillary hemangioma that had grown so rapidly as to cause a cleft of the ala.[16] The hemangioma involuted after one treatment, with lessening of the nasal cleft. We subsequently reported a larger series of capillary or cavernous hemangiomas successfully treated with YAG laser photocoagulation plus the intralesional administration of steroid.[15]

The YAG laser may also be used in interstitial laser photocoagulation.[17] In this technique, a bare laser fiber is passed directly into the depths of the hemangioma, and localized photocoagulation is done at various depths and levels in a radial spoke-like fashion. This intralesional photocoagulation results in dramatic shrinkage and fibrosis of the lesion. The YAG laser may also be used as a "light scalpel" because of its ability to cut and coagulate at the same time. Combined with sapphire tips in a contact mode, this laser has been reported to be particularly effective in removing vascular lesions.[18,19] We have combined YAG laser excision with previous arteriography plus superselective embolization to achieve further hemostasis.[20,21]

Conclusion

We treated 22 patients with nasal hemangioma or vascular malformations by various lasers and laser modalities with satisfactory reconstructive and cosmetic results. Although natural involution may occur, growth and hypertrophy may cause a distortion of the nasal architecture or present emotional problems necessitating treatment. The argon, tunable dye, or YAG laser may be used to photocoagulate thin or developing lesions. Thicker or larger lesions may require interstitial laser photocoagulation, the administration of intralesional or parenteral steroids, or surgical excision accomplished with contact sapphire scalpel tips. Contact YAG laser excision plus arteriography and superselective embolization may also be used to control lesion growth and vascularity.

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* * *

The Prophet in His Own Country

Yes, I grew up in Rutherford,
little New Jersey town,
lots of weddings and funerals.
It was the Twenties,
before the world went gray.
Sure, I knew Doc Williams:
he took care of me
when I was a little girl.
I remember the doctor
with gentle eyes
Ma took us to
when our heads felt hot.

He wrote poems?
Wouldn't have thought
he'd have time
what with seeing all those babies.
A book about Paterson?
My husband's from there;
maybe it mentions folks
he used to know.
Say, I ought to read it
some time.

D. A. FEINFELD, MD©
Scarsdale, New York

Articles

Staphylococcus aureus Septic Arthritis in Patients on Hemodialysis Treatment

SARAH SLAUGHTER, MD; RONALD J. DWORKIN, MD; DAVID N. GILBERT, MD; JAMES E. LEGGETT, MD; STEPHEN JONES, MD; RICHARD BRYANT, MD; *and* MICHAEL A. MARTIN, MD, *Portland, Oregon*

We retrospectively reviewed hospital discharge diagnoses of septic arthritis over an 11-year period (1982 through 1992) at 3 medical centers; 11 episodes of septic arthritis were identified in patients on hemodialysis treatment. Of the 11 episodes, 9 were caused by *Staphylococcus aureus*; in 8 of 9, the blood cultures were positive for the organism and the infection was monoarticular. Concurrent infection of the dialysis access site occurred in 4 cases. Two patients died (22%). We postulate that repeated skin trauma and contact with health care personnel and facilities result in a high rate of nasal carriage of *S aureus* and, hence, an increased risk of bacteremia with its attendant complications such as septic arthritis. The use of mupirocin nasal ointment is reported to eradicate or suppress carriage in a high percentage of patients; some studies report that long-term suppressive therapy reduces the frequency of *S aureus* bacteremia.

(Slaughter S, Dworkin RJ, Gilbert DN, et al: *Staphylococcus aureus* septic arthritis in patients on hemodialysis treatment. West J Med 1995; 163:128-132)

A case of a patient on hemodialysis treatment in whom *Staphylococcus aureus* septic arthritis developed prompted inquiry into the regional frequency of this serious disorder. Only one previous article has addressed this subject.[1] At three large tertiary care centers, nine patients with this disease were identified over an 11-year period. Septic arthritis is a complication of *S aureus* bacteremia that in turn results from a high rate of nasal and skin carriage of *S aureus*. The literature indicates that the frequency of invasive *S aureus* disease in dialysis-dependent patients may be reduced substantially by appropriate antimicrobial prophylaxis.

Patients and Methods

Patient hospital discharge records with ICD-9 [*International Classification of Diseases*, 9th revision] codes for septic arthritis and hemodialysis were searched over an 11-year period (1982 through 1992) at three local tertiary care medical centers: Providence Medical Center, Good Samaritan Hospital and Medical Center, and Oregon Health Sciences University Medical Center, Portland. In all, 11 episodes of septic arthritis in 10 patients on hemodialysis treatment were identified, 9 of which were caused by *S aureus*. Patient records were analyzed for patient demographics, joints involved, microbiologic data, length of time on hemodialysis, type of dialysis access, evidence of concurrent infection of the dialysis access site, a history of previous *S aureus* infection(s), management of the infection, and patient outcome.

Summaries of Selected Cases

Patient 1

The patient, an 81-year-old woman with diabetes mellitus and ischemic cardiomyopathy, had been on hemodialysis treatment for eight months when malaise developed without localizing symptoms or signs. Four days later, she presented to the emergency department with pain in her right arm, and analgesics were administered. The following day she was admitted to the hospital with fever, left arm and shoulder pain, and fluctuance of the left shoulder. Cultures of left shoulder joint fluid and blood were positive for *S aureus*, and an initial therapy regimen of vancomycin hydrochloride and gentamicin sulfate was changed to nafcillin sodium and rifampin. Despite appropriate antibiotic therapy, the patient gradually became hypotensive and died in septic shock on the fourth hospital day.

Patient 2

The patient, a 61-year-old woman on hemodialysis therapy for many years, had a flulike illness with an increase in chronic arthralgias of her hips, shoulders, and knees. She had previously had multiple infections of the polytetrafluoroethylene arteriovenous dialysis access graft of her left forearm, including two episodes of *S aureus* bacteremia. Although the old graft was still present, a new graft had been placed in the right forearm six weeks before admission. Two days after her flulike illness began, she was admitted to the hospital. Blood cultures

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obtained on admission were subsequently positive for *S aureus* resistant in vitro only to penicillin G. Because of an allergy to penicillin and cephalosporins, a regimen of vancomycin was started. Persistent fever and positive blood cultures over the next six days prompted removal of the graft despite the absence of physical findings; culture of specimens obtained intraoperatively grew *S aureus*. Arthralgias and fever persisted; three weeks after admission, the right shoulder was aspirated and the aspirate grew *S aureus*. Daily shoulder arthrocentesis yielded culture-positive specimens for the next five days. For this reason, gentamicin was added to the regimen of vancomycin, and this therapy was continued for nine days as the patient's temperature and leukocyte count returned to normal. Subsequently, the gentamicin therapy was stopped, but vancomycin was continued for a total of six weeks after the initial shoulder aspiration. The patient was discharged after a 2½-month hospital stay.

Patient 3

This 57-year-old woman with end-stage renal disease had a first polytetrafluoroethylene dialysis access graft placed in her left forearm. The graft clotted, and a thrombectomy was done a week after placement. The surgical wound continued to drain, and two months later she was admitted to the hospital with a wound infection, bacteremia, and left lower lobe pneumonia due to *S aureus*. She complained of left anterior chest pain, but no physical signs other than chest wall tenderness were found. On the fifth hospital day, a fluctuant mass was seen over the left sternoclavicular joint. Purulent fluid was aspirated, and the cultures grew *S aureus*. The patient was initially treated with cefazolin for five days; subsequently, she was switched to vancomycin, which was continued for six weeks. In addition, the infected portion of the graft was excised.

Results

Nine episodes of *S aureus* septic arthritis in eight dialysis patients are summarized in Table 1. Three patients had arteriovenous fistulas, four had polytetrafluoroethylene (Gore-Tex) arteriovenous grafts, and one had a cuffed dialysis catheter (Perma-Cath). Concurrent access infection was documented in four cases; three of these involved polytetrafluoroethylene grafts, and one involved a cuffed catheter. In another patient, *S aureus* infection of the arteriovenous fistula occurred 2½ months before an admission for septic arthritis. The access did not appear infected at the time of the episode of septic arthritis; however, no blood cultures were done to definitively exclude this source. In the other eight episodes, blood cultures grew *S aureus*. Two patients died of *S aureus* sepsis, one on the fourth hospital day and one on the tenth hospital day, for a mortality of 22%. The six surviving patients received courses of intravenous antibiotics ranging from one week to six weeks. All *S aureus* isolates were methicillin-sensitive. The choice of antibiotics varied, but in most cases consisted of a β-lactam plus an aminoglycoside for early therapy, followed by a longer course of a β-lactam or vancomycin. Four patients had previous admissions for *S aureus* infections, including five episodes of bacteremia and one of infection of the arteriovenous fistula in which concurrent blood cultures were sterile. The two patients who died had been on hemodialysis treatment a relatively short period of time (2 months and 8 months), and this was their first *S aureus* infection. None of the patients had nasal or skin cultures for the identification of *S aureus* carriage, and none were on prophylactic antibiotic regimens designed to decrease the risk of *S aureus* infections.

TABLE 1.—*Characteristics of 8 Hemodialysis Patients With 9 Episodes of* Staphylococcus aureus *Arthritis*

Characteristic	*Patients, No.*	*Episades, No.*
Sex		
Male	3	
Female	5	
Age range, yr	57-81	
Time on dialysis	?days to 14 years	
Joints affected		
Monoarticular		8
Biarticular		1
Above diaphragm		8
(Shoulder)		(3)
(Sternoclavicular)		(2)
(Wrist)		(2)
(Acromioclavicular)		(1)
Below diaphragm		2
(Ankle)		(1)
(Wrist)		(1)
Blood culture results		
Positive for *S aureus*		8
Not done		1
Concurrent dialysis access infection		4
Surgical incision and drainage		4
Multiple aspirations		3
Predominant antimicrobial therapy		
Vancomycin ± aminoglycoside ± rifampin	7*	
Nafcillin plus rifampin	1†	
Cefazolin only	1	

*One of the 7 patients died.
†Patient died.

Discussion

In our review of hospital discharges for septic arthritis, we were struck by the clustering of cases in patients on long-term hemodialysis therapy and by the predominance of *S aureus* as the etiologic agent. We then sought episodes of septic arthritis in hemodialysis patients at two other tertiary care medical centers. Over an 11-year period, 9 of 11 joint infections were due to *S aureus*. The high mortality (22%), protracted hospital stays, and paucity of previous reports in the literature stimulated inquiry into whether it is possible to reduce the risk of this serious illness.

We found one published study of septic arthritis in hemodialysis patients.[1] Six cases of septic arthritis were reported in five patients; *S aureus* was the pathogen in four.

Blood cultures grew *S aureus* in three patients, and the access device grew *S aureus* in the fourth. Five of the six joints infected with *S aureus* were above the diaphragm. Three patients had previous infections of the access site. Two of the patients had several previous episodes of *S aureus* infection. All patients in this series survived.

Admissions for septic arthritis in the series described in the previous paragraph made up 2% of all admissions of patients on hemodialysis therapy during the study period. In comparison, admissions for septic arthritis are much less common in nondialyzed patients. In one report, hospital admissions for all patients at King County and Seattle, Washington, Veterans Affairs hospitals during a five-year period were reviewed, and an overall incidence of septic arthritis of 0.022% was found.[2]

We reviewed the literature to identify some of the reasons for the increased incidence of joint infections in patients on hemodialysis therapy and for the preponderance of *S aureus*. Hematogenous seeding is the most common pathogenesis of joint infection.[3] Hemodialysis patients have frequent vascular access infections[4-10] and, hence, have a greater risk of their joints becoming infected. In addition, hemodialysis patients are reported to have a high incidence of joint calcification and other abnormalities such as hemarthrosis and chronic capsulitis.[11] A diseased joint may be more susceptible to invasion when bacteremia occurs. The reason for a predisposition for infection in joints above the diaphragm in these patients is unclear. Perhaps it reflects "downstream" embolization in some cases. We were unable to correlate clearly the location of arteriovenous access to involved joints, however.

The incidence of bacteremia due to all organisms varies from 0.7 to 1.5 episodes per 100 patient-dialysis months.[4-10,12,13] The percentage due to *S aureus* varied from 32% to 80%. The dialysis access site is incriminated as the primary source of infection in 49% to 100% of the episodes. *Staphylococcus aureus* is the most frequent organism cultured from the blood, representing 32% to 80% of the bacteremic episodes. In contrast, *S aureus* accounts for only 11% of community-acquired and 20% of hospital-acquired cases of bacteremia in all patients.[14] The reported mortality for all cases of bacteremia is about 20%, and for *S aureus* bacteremia it is similar at 8% to 16%. Of those patients with bacteremia, 3% or less suffer hematogenous septic arthritis.[10] Other frequently encountered hematogenous complications include pulmonary emboli (3.5% to 16%), empyema (1% to 2.7%), and central nervous system infections (2% to 4.5%). Of interest, infective endocarditis is reported in only 3.5% to 9%.[8-10] Hence, *S aureus* infection, including septic arthritis, is a major risk for patients on hemodialysis.

Colonization of the nose and skin (including the vascular dialysis access site) is the presumed portal of entry for *S aureus*. Repeated skin trauma, contact with colonized hospital personnel, the presence of a foreign body, and possibly immune defects are proposed explanations for the high rate of colonization. Once the skin barrier is broken, the clearance of transient bacteremia may be impaired in a patient with uremia. For example, macrophage Fc receptors bind immunoglobulin G-coated organisms, and these receptors are substantially impaired in patients with uremia.[15]

Numerous studies have reported an increased rate of staphylococcal nasal colonization in patients on hemodialysis treatment. Nasal colonization rates in these patients are reported to vary between 40% and 81% as compared with 20% to 40% carriage rates among nondialyzed patients.[5,6,16-20] *Staphylococcus aureus* colonization rates of patients undergoing continuous ambulatory peritoneal dialysis are reported to be between 39% and 45%.[21,22] Hence, 40% or more of all dialysis patients are at risk for invasive *S aureus* disease.

Hemodialysis patients who are *S aureus* carriers have more staphylococcal infections than noncarriers. In a retrospective study of 40 patients, 10 of the 14 with *S aureus* colonization (71%) had serious staphylococcal infections, although only 10 of 26 patients (38%) without colonization had staphylococcal infections.[23] In a prospective study of *S aureus* carriage in hemodialysis patients, 7 *S aureus* infections occurred in 31 carriers (22%) versus 2 infections in 19 noncarriers (11%).[16] In a second prospective controlled trial, a 46% incidence of *S aureus* infections was reported in carriers versus 11.5% in noncarriers ($P < .01$). The phage type of the infecting organism matched the carriage organism in 93% of the carriers in whom infection developed.[18] Hence, it seems reasonable to consider possible ways of preventing or controlling the magnitude of *S aureus* colonization.

Prevention

Invasive disease could be prevented in one of several ways: preventing *S aureus* colonization, eradicating existing colonization, or decreasing the density (and, it is hoped, the invasion risk) of colonizing *S aureus*. A variety of agents, both oral and topical, have been used to try to eradicate staphylococcal nasal and skin carriage. Topical gentamicin sulfate, vancomycin hydrochloride, and bacitracin and oral cloxacillin sodium, tetracycline, cephalexin hydrochloride, and erythromycin are ineffective.[24] Intravenous vancomycin is likewise ineffective.[18] In contrast, oral rifampin, in combination with topical bacitracin, reduces the short-term incidence of both *S aureus* nasal carriage and *S aureus* infections.[18] Unfortunately, rifampin possesses several features that make it less attractive as a prophylactic agent. It can be hepatotoxic, it stains body secretions orange, and when used intermittently, it can be associated with flulike symptoms. In addition, the use of rifampin alone is known to induce resistance in most bacterial species.

Topical mupirocin (pseudomonic acid) has shown promise as an agent for suppressing or eliminating the nasal carriage of both methicillin-sensitive and resistant *Staphylococcus aureus* in a variety of populations (Table 2). It was applied two to four times a day for three to five days, and at the end of therapy, negative cultures were reported in 74% to 100% of one study group. For as long as three months after treatment, the percentage of patients with persistent eradication ranged from 41% to 82%.[19,25-29]

TABLE 2.—*Short-Term Regimens of Mupirocin for the Treatment of* Staphylococcus aureus *Nasal Carriage*

Source	Treatment Regimen	Treatment Group	No.	S aureus Eliminated at End of Treatment, %	S aureus Eliminated at Follow-up, %
Casewell and Hill, 1985[32]	Daily × 5 days	Hospital staff volunteers	32	100	At 3 mo: 57
Holton et al, 1991[26]	3 × day × 5 days	Hemodialysis patients	22	77	At 1 mo: 46; at 2 mo: 32; at 3 mo: 23
Reagan et al, 1991[19]	2 ×/day × 5 days	Health care workers	34	97	At 3 mo: 71
Redhead et al, 1991[27]	Variable: ≤4 ×/day × 3-5 days*	Hospital inpatients, outpatients, and staff	766	97†	No follow-up cultures
Doebbeling et al, 1992[28]	2 ×/day × 5 days	Healthy volunteers	143	91	At 1 mo: 82
Scully et al, 1992[29]	2 ×/day × 5 days	Healthy medical center staff	34	74	At 1 mo: 41

*Until cultures showed elimination.
†628 patients had methicillin-resistant *S aureus*, which was eliminated in 97%.

One study focused on long-term suppression in hemodialysis patients (Table 3). Mupirocin was applied three times a day for 5 to 14 days and then three times a week (at dialysis) for 6 to 9 months.[17,30] Nasal cultures during this time were negative for *S aureus* in 94% to 100% of the patients. The incidence of *S aureus* bacteremia was reduced 4.26-fold in the carriers treated with mupirocin versus the control group. Only one episode of *S aureus* bacteremia occurred in 41.1 years of patient follow-up in the treatment group (incidence of 0.0227 per patient year) as compared with 18 episodes of *S aureus* bacteremia during 185.8 patient years in the control group (incidence of 0.0969 per patient year; $P = .08$). In another study, the cost of mupirocin prophylaxis was calculated at $266 per patient year, as compared with a cost of $896 per patient year at risk for the treatment of *S aureus* bacteremia. It was concluded that mupirocin prophylaxis is cost-effective.

In studies in Europe, mupirocin resistance did not emerge, despite long-term (9 months) treatment, although resistance has been described by others.[31-33] Low-level resistance is less important because the concentration of mupirocin in the ointment is 20,000 μg per ml. High-level resistance—minimal inhibitory concentration >700 μg per ml—correlates with the clinical failure to eradicate *S aureus*.[34-36] To date, the reported incidence of high-level mupirocin resistance among *S aureus* organisms remains low.[37] Recent reports from hospitals and long-term care facilities in the United States describe both low- and high-level resistance, however.[29,34,38]

Patients on hemodialysis treatment are at an increased risk of *S aureus* colonization with the subsequent complications of vascular access infection, bacteremia, and septic arthritis and attendant dangers of protracted morbidity and mortality. Hence, it seems reasonable to culture the anterior nares of hemodialysis patients periodically (perhaps monthly). In those patients with positive cultures, implementation of the regimen described elsewhere (Table 3)[17,30] may reduce the number of subsequent *S aureus* infections. Patients receiving applications of mupirocin three times a week should have cultures repeated at one- to three-month intervals; if *S aureus* is detected, it is desirable to have the laboratory capability to determine whether mupirocin resistance has developed. Future studies should address the problem of the development of mupirocin resistance and measures that might attenuate the rate of development of resistance in an individual patient or in groups of patients in hemodialysis units.

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TABLE 3.—*Long-Term Regimens of Mupirocin for the Treatment of* Staphylococcus aureus *Nasal Carriage in Hemodialysis Patients*

Source	Treotment Regimen	Hemodialysis Patients, %	S aureus Eliminated With Suppressive Therapy, %
Boelaert et al, 1989[30]	3 ×/day × 2 wk, then 3 ×/wk for 9 mo	16	At 2 wk: 100; during later treatment: 94
Boelaert et al, 1991[17]	3 ×/day × 5 days, then 3 ×/wk for 6 mo	31	At 3 mo: 100; at 6 mo: 100

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Prevalence and Reversibility of the Hepatopulmonary Syndrome After Liver Transplantation

The Cleveland Clinic Experience

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To ascertain the prevalence and reversibility of the hepatopulmonary syndrome, we reviewed the cases of 98 patients undergoing liver transplantation at the Cleveland (Ohio) Clinic Foundation from June 1988 through July 1992 and identified 4 patients with clinically recognized hepatopulmonary syndrome (prevalence 4%). All 4 patients ultimately had complete reversal of their disorder. As reviewed herein, the prevalence of the hepatopulmonary syndrome in the current series is lower than in previous reports, possibly reflecting a dependence on its clinical recognition in this series rather than the use of routine screening tests. This report confirms previous experience that the hepatopulmonary syndrome may be reversible after transplantation.

(Stoller JK, Lange PA, Westveer MK, Carey WD, Vogt D, Henderson JM: Prevalence and reversibility of the hepatopulmonary syndrome after liver transplantation—The Cleveland Clinic experience. West J Med 1995; 163:133-138)

The hepatopulmonary syndrome is characterized by a triad of impaired arterial oxygenation, hepatic dysfunction, and the presence of intrapulmonary vascular dilatations.[1-5] Clinical features include dyspnea, orthodeoxia, tachypnea, cyanosis, and digital clubbing.

Despite earlier impressions that the hepatopulmonary syndrome is irreversible and that it is a contraindication to liver transplantation (because posttransplantation hypoxemia could exacerbate graft failure),[3,6-9] recent observations suggest that the syndrome can resolve after liver transplantation.[10-20] In the context that the pathogenesis of the hepatopulmonary syndrome remains unknown, however, predicting reversal after liver transplantation currently remains impossible.

This study was undertaken to assess the frequency and time course of the reversal of the hepatopulmonary syndrome following liver transplantation. Because overall estimates of the prevalence of the syndrome vary widely, another goal of this research was to examine its prevalence among liver transplantation candidates referred to the Cleveland (Ohio) Clinic Foundation.

Patients and Methods

To identify patients with the hepatopulmonary syndrome before undergoing liver transplantation and also the group in whom posttransplantation reversibility could be assessed, we reviewed retrospectively the roster of all patients undergoing liver transplantation at the Cleveland Clinic Foundation from June 1988 through July 1992. Over this 49-month period, 98 patients underwent liver transplantation at our institution. The subjects of the current report are the 4 patients in whom the hepatopulmonary syndrome was suspected (and subsequently confirmed) by their managing physicians. Although routine screening for the syndrome—by the physiologic assessment of shunt fraction, by imaging using technetium Tc 99m-labeled macroaggregated albumin or contrast-enhanced echocardiography, or both—was not part of our routine pretransplantation evaluation protocol until after the current study was completed (November 1993), our previously reported experience with a patient whose hepatopulmonary syndrome and associated digital clubbing reversed after liver transplantation heightened our suspicion for the syndrome.[11]

The following criteria were used for diagnosing the hepatopulmonary syndrome in this series:

- Impaired oxygenation, defined as an elevated alveolar-arterial oxygen gradient ($P_{AO_2} - Pa_{O_2}$) for age (using a maximal normal age-specific value of $P_{AO_2} - Pa_{O_2}$ as age ÷ 4 + 4);
- The presence of chronic liver dysfunction; and
- Evidence of a right-to-left shunt, based on the results of radionuclide scans using ^{99m}Tc-macroaggregated albumin, contrast-enhanced echocardiography, or both.

Radionuclide scans using ^{99m}Tc-macroaggregated albumin were done using standard techniques.[21] Specifically, after the administration of 4 mCi of ^{99m}Tc-macroaggregated albumin (mean particle diameter, 20 to 50 μm), scans were taken over the kidney and brain to detect particles bypassing the pulmonary capillaries (the smaller diameter [8 to 15 μm] of which would trap the

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macroaggregated albumin particles). The appearance of radionuclide in the brain, kidneys, or both denotes the qualitative presence of a right-to-left shunt.

Contrast-enhanced surface echocardiography was performed using standard echocardiographic techniques (Sonos-1000, HP-77020A, Hewlett Packard, Andover, Massachusetts). Contrast consisted of microbubbles (60 to 90 μm) created by administering a hand-agitated saline solution or indocyanin intravenously. The appearance of microbubbles or contrast in the left atrium or the left ventricle (or both) three to six cardiac cycles after their appearance in the right atrium denotes an intrapulmonary right-to-left shunt.[22,23] Transesophageal echocardiography was not routinely performed.[24] As previously reported, one of the four patients underwent pulmonary angiography and was found to have a type 1 angiographic pattern (diffuse, "spongy" vascularity).[11,25]

Other tests included arterial blood gas measurements, both while the patient was breathing room air (either standing or supine as indicated) or after the patient had breathed 100% oxygen. The shunt fraction was determined by obtaining an arterial blood specimen after the patient breathed 100% oxygen through a tight-fitting face mask for at least 20 minutes. The shunt fraction was calculated according to a published nomogram that assumes an arteriovenous oxygen content difference of 5 mg per dl.[26]

Orthodeoxia was defined as a decline in room-air arterial oxygen tension of 10 mm of mercury or more when the patient was standing (versus the baseline seated or supine value). The room-air $P_{AO_2} - Pa_{O_2}$ gradient was calculated according to a standard formula using a respiratory quotient value of 0.8. Age-specific normal values were calculated using the formula age ÷ 4 + 4.[27]

Static pulmonary function tests included spirometry and the measurement of lung volumes and steady-state diffusing capacity. This spirometry was done using a pneumotachygraph-based spirometer (Model TL, Spinnaker, and Excel, Cybermedic, Inc, Boulder, Colorado) without inhaled bronchodilators. We recorded the highest spirometric values based on three acceptable spirometry maneuvers, as defined by American Thoracic Society criteria.[28] Predicted values for the forced expiratory volume in 1 second and the forced vital capacity were based on published predictive equations.[29] Lung volumes were determined by helium dilution using published predictive equations.[30] With the patient seated, the lungs' diffusing capacity for carbon monoxide was measured using a single-breath technique and comparing with predicted normal values.[31]

Results

Of 98 cases of liver transplantation reviewed, 4 patients were suspected clinically by their managing physicians of having the hepatopulmonary syndrome. In each patient, further pretransplantation evaluation confirmed the presence of the syndrome, yielding a prevalence of clinically suspected hepatopulmonary syndrome of 4% (4/98) in this series. Patient 1 was the subject of an earlier report from our group.[11]

Characteristics of these four patients with the hepatopulmonary syndrome who subsequently underwent liver transplantation are summarized in Table 1. Their mean age was 33.5 years (range, 5 to 52). All patients had limited exercise tolerance and digital clubbing. Cutaneous spider angiomata were noted in three patients. Orthodeoxia was present in one of the two patients for whom matched supine and standing room-air arterial blood gas values were available.

The pretransplantation physiologic features of these four patients are summarized in Table 2. Among the three patients with available measurements of diffusing capacity, values were uniformly low (mean, 51.6% predicted; range, 34% to 64% of predicted). Similarly, among the three patients with available room-air arterial blood gas values, the $P_{AO_2} - Pa_{O_2}$ gradients were elevated in all three (mean value, 58.1 mm of mercury; range, 43 to 66 mm of mercury). In the fourth patient, the pretransplantation Pa_{O_2} with the patient receiving 6 liters of transtracheal oxygen was 45 mm of mercury. The mean pretransplantation shunt fraction was 18.7% in the three patients studied (range, 18% to 20%).

As shown in Figure 1, the hepatopulmonary syndrome resolved in all four patients following liver transplantation. The reversal of the right-to-left shunt was demonstrated by a return to normal shunt fraction measurements in three patients following liver transplantation and, in patient 2, who was 5 years old, by less invasive contrast-enhanced echocardiography. The mean posttransplantation shunt fraction was 4.5% (range, 3.5% to 5.1%). The interval over which the hepatopulmonary syndrome was

TABLE 1.—*Characteristics of Patients With the Hepatopulmonary Syndrome Undergoing Liver Transplantation*

Patient	*Age at Tronsplantation*	*Sex*	*Diagnosis*	*Digital Clubbing*	*Orthodeoxio**	*Transplantation Dote*
1.....	38	F	Primary biliary cirrhosis	Yes	No	6/12/88
2.....	5	F	Postnecrotic cirrhosis	Yes	NA	7/20/90
3.....	52	M	Laennec's cirrhosis	Yes	NA	6/28/91
4.....	39	F	Autoimmune chronic active hepatitis	Yes	Yes	7/29/92

NA = data not available

*Orthodeoxia is defined as a decline in the Pa_{O_2} value with the patient breathing room air of 10 mm of mercury from supine to standing.

TABLE 2.—*Pretransplantation Physiologic Measurements*

Patient	FEV_1, % Predicted	FEV_1/FVC, %	TLC, % Predicted	D_{LCO}, % Predicted	Po_{O_2}, mm of mercury	$P_{AO_2} - Pa_{O_2}$, mm of mercury	Shunt Fraction, %*	Controst Echo
1.....	68	78	74	64	62	43	18	Intrapulmonary right-to-left shunt present
2.....	NA	NA	NA	NA	36	66.5	NA	Intrapulmonary right-to-left shunt present
3.....	64	67	86	57	43	66	18	Intrapulmonary right-to-left shunt present
4.....	59	77	NA	34†	NA‡	NA	20	NA

D_{LCO} = diffusing capacity of the lungs for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, NA = not available, $P_{AO_2} - Pa_{O_2}$ = alveolar-arterial oxygen gradient, TLC = total lung capacity

*Value is obtained with the patient sitting.

†Not corrected for the hemoglobin level.

‡Pa_{O_2} = 45 mm of mercury while patient was receiving oxygen transtracheally at 6 liters/minute.

documented to resolve ranged from 1 to 8 months, when posttransplantation assessments were done.

Figure 2 depicts the change in the $P_{AO_2} - Pa_{O_2}$ gradient values before and after transplantation in all three patients while they were breathing room air. While patient 4 was receiving 6 liters of transtracheal oxygen before transplantation, the Pa_{O_2} was 45 mm of mercury; after transplantation the $P_{AO_2} - Pa_{O_2}$ gradient was 29.7 mm of mercury. In the absence of demonstrable right-to-left shunting after liver transplantation to suggest persistent hepatopulmonary syndrome, persistent elevation of the $P_{AO_2} - Pa_{O_2}$ gradient was thought to indicate other causes of abnormal oxygenation, such as persistent ventilation/perfusion mismatching.

Discussion

The current study elicited the following findings:

- The prevalence of clinically suspected hepatopulmonary syndrome was 4% among this group of liver transplant recipients.
- The hepatopulmonary syndrome was uniformly reversible following liver transplantation in the four patients in whom it was detected in this series.
- The time to detected reversal of the hepatopulmonary syndrome was one to eight months in this series.

The estimated prevalence of the hepatopulmonary syndrome of 4% in the current series is lower than other available estimates, which range from 13% to 47%.[23,32] Specifically, a group of 40 liver transplant candidates were systematically screened for the hepatopulmonary syndrome.[32] The investigators noted that 13% (5 of 38) of these patients had echocardiographic evidence of intrapulmonary vascular dilatations, the hallmark of the syndrome. In another series, 53 liver transplant candidates were studied, and evidence of intrapulmonary right-to-left shunting was demonstrated in 25 (47%) by contrast-enhanced echocardiography.[23] That our prevalence estimate is lower than that of others probably reflects the dependence on the clinical recognition of the hepatopulmonary syndrome in the current series rather than systematic screening with contrast-enhanced echocardiography or radionuclide scans, as was undertaken in the two other series cited. Evidence of intrapulmonary right-to-left shunting by contrast-enhanced echocardiography has been shown in patients lacking clinical features of the hepatopulmonary syndrome such as orthodeoxia, platypnea, or both.[32] Furthermore, it has been observed that contrast-enhanced echocardiograms positive for right-to-left intrapulmonary shunting in 10% of cirrhotic patients with Pa_{O_2} values exceeding 70 mm of mercury suggest a disparity between the anatomic evidence of right-to-left shunt and physiologic evidence of venous admixture.[32] Discordance was also reported recently between the results of contrast-enhanced echocardiography and physiologic shunt studies in 60 liver transplant candidates.[33] Of the 26 patients with discordant results (such as positive echocardiographic study for intrapulmonary right-to-left shunt but shunt less than 5%), 12 (20%) had positive contrast-enhanced echocardiograms but normal shunt studies and 14 (23%) had positive shunt studies but normal echocardiograms.

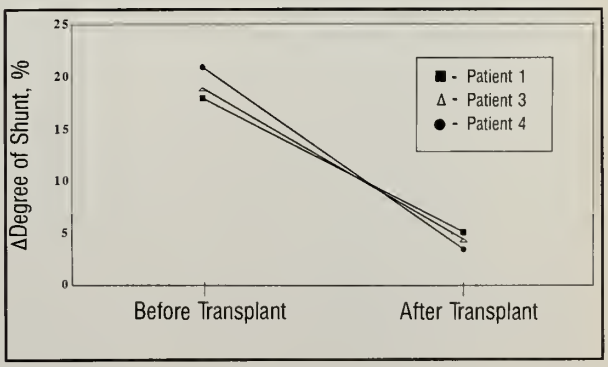

Figure 1.—The graph depicts the results of shunt fraction before and after liver transplantation in the 3 patients in whom both measurements were available. Shunt fractions decreased markedly in all 3 patients. The range of time between shunt assessments was 1 month in patient 1 to 8 months in patient 4.

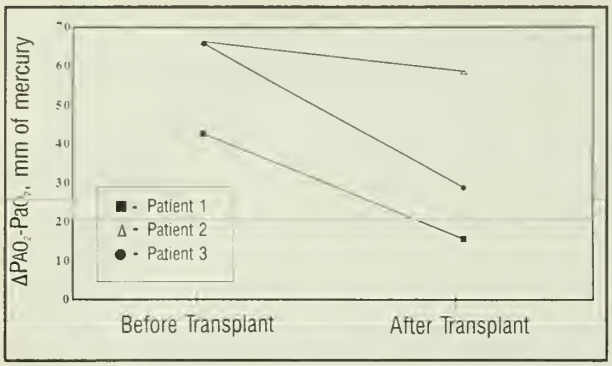

Figure 2.—The graph shows the results of the alveolar-arterial oxygen gradient ($P_{AO_2} - P_{aO_2}$) taken with the patient breathing room air in the 3 patients in whom both measurements were available. The mean $P_{AO_2} - P_{aO_2}$ decreased after liver transplantation from 58.1 to 33.4 mm of mercury, but remained abnormally elevated.

In the context that some persons may have evidence of intrapulmonary vascular dilatation with little impairment of gas exchange, we suspect that systematic screening of the 98 patients in this series would have detected additional patients whose hepatopulmonary syndrome was more clinically subtle than in the 4 patients reported here. To address this suspicion, current practice at the Cleveland Clinic Foundation is to evaluate all prospective liver transplantation candidates with two-dimensional surface contrast-enhanced echocardiography and shunt determinations done with the patient breathing 100% oxygen. Transesophageal echocardiography, which we have used to identify the site of intrapulmonary vascular dilatation by localizing contrast bubbles in specific pulmonary veins,[24] has not been performed routinely. Similarly, until the therapeutic relevance of distinguishing between a type 1 (diffuse "spiderlike" vessels) and a type 2 (discrete vascular changes) angiographic pattern is better understood, we have reserved the use of pulmonary angiography for standard indications—suspected pulmonary embolism or large arteriovenous malformations.

Our finding that the hepatopulmonary syndrome was universally reversible following liver transplantation in this series is also at odds with existing observations. Table 3 reviews the frequency with which intrapulmonary shunting caused by the hepatopulmonary syndrome lessened or reversed following liver transplantation in available series and indicates that 52% complete reversal and 43% partial abatement occurred.[8,10-19,32,34-40] Although some reports do demonstrate failure of the hepatopulmonary syndrome to resolve or to lessen at all following liver transplantation (Table 3), we suspect that "publication bias"[41] has inflated

TABLE 3.—*Review of Available Reports Regarding Reversal or Improvement of Intrapulmonary Shunt in Liver Disease*

Source	Potients, No.	Liver Disease	Transplanted, No.	Resolved Partial (P) vs Tatal (T), %
Silverman et al, 1968[34]	2	NS	0	T: 50 (after liver recovery in 1 pt)
Starzl et al, 1968[10]	3	NS	3	P: 100
Stanley and Woodgate, 1972[35]	1	Fascioliasis	0	T: 100 (after liver recovery)
Chen et al, 1984[36]	1	Alcoholic cirrhosis	0	T: 100 (after liver recovery)
Salem et al, 1989[37]	1	NS	0	P: 100 with somatostatin analogue
Shijo et al, 1989[38]	1	Cryptogenic cirrhosis	0	P: 100 after liver recovery
Eriksson et al, 1990[12]	6	Mixed	6	T: 83*; P: 17
Krowka et al, 1990[32]	1	Chronic active hepatitis	1	0
Mews et al, 1990[8]	1	Wilson's	1	0
Stoller et al, 1990[11]	1	Primary biliary cirrhosis	1	T: 100
Dimand et al, 1991[14]	3	Mixed; portal hypertension	3	P: 67; T: 33
Levin et al, 1991[13]	1	Extrahepatic biliary atresia	1	T: 100
McCloskey et al, 1991[17]	1	Cryptogenic cirrhosis	1	T: 100
Cadranel et al, 1992[39]	1	Nodular regenerative hyperplasia	0	T: 100 after medical therapy
LaBerge et al, 1992[15]	2	Cirrhosis due to extrahepatic biliary atresia	2	T: 100
Barry et al, 1993[20]	7	NS	7	T: 28; P: 72
Scott et al, 1993[16]	6	NS	6	P: 50; T: 50
Itasaka et al, 1993[18]	1	Cryptogenic cirrhosis	1	T: 100
Schwarzenberg et al, 1993[19]	1	α_1-Antitrypsin deficiency	1	T: 100
Shijo et al, 1993[40]	1	Macronodular cirrhosis	0	P: 100 (spontaneous improvement)
Total	42		32	Partial improvement: 43 Total improvement: 52

NS = not specified

*As determined by the alveolar-arterial oxygen gradient.

the prevalence of reported reversibility, especially because the concept that the hepatopulmonary syndrome can be reversed has gained recognition only over the past several years (since 1989). Because no large series evaluating the reversibility of hepatopulmonary syndrome after liver transplantation is available, case reports or small case series of patients with the hepatopulmonary syndrome failing to improve after liver transplantation seem less newsworthy and, therefore, less likely to be submitted or accepted for publication. To the extent that the 4 patients in this report with reversible hepatopulmonary syndrome represent only a fraction of all such patients among our 98 liver transplant recipients, we suspect that our data may overestimate the frequency with which the hepatopulmonary syndrome reverses after liver transplantation.

Finally, our observation that the hepatopulmonary syndrome resolved within eight months after liver transplantation is consistent with observations by others.[10-20] As presented in Table 4, some reports document improvement in the shunt fraction within days of liver transplantation, whereas others show more delayed resolution (2 to 14 months). Because none of the available series has done testing for the hepatopulmonary syndrome at frequent, predetermined intervals following transplantation, some of the splay in the observed time course of resolution may reflect managing physicians' decisions to defer postoperative testing for the syndrome until patients were beyond the immediate postoperative period. Also, in the absence of a specified posttransplantation protocol for retesting for the syndrome, clinicians are likely to reassess only when clinical improvement is evident enough to justify the inconvenience, expense, and morbidity of repeated testing. In patient 1 in the current series (whose case was reported previously[11]), the resolution of clinical features of the hepatopulmonary syndrome was evident within 37 days after liver transplantation (that is, by the resolution of digital clubbing and a reduction in shunt fraction), but was incomplete by the second postoperative day (based on the persistence of a positive contrast-enhanced echocardiogram at 34 hours).

Several shortcomings of the current study are evident. Like most available series, pretransplantation screening for the hepatopulmonary syndrome was not uniform in this series, so that underdetection of the syndrome is

TABLE 4.—*Time to Resolution of the Hepatopulmonary Syndrome Following Liver Transplantation in Available Series*

Source	Patients, No.	Age, yr	Disease	Po_2, mm of mercury		Shunt, %		Time to Resolution
				Room Air	100% Oxygen	100% Oxygen*	^{99m}Tc†	
Starzl et al, 1968[10]	3	<20 mo	Mixed	85-88‡	NR	50	NR	Decreased shunt (5%-15%) immediately in 2 patients and after 10 days in the 3rd
Eriksson et al, 1990[12]	6	18-45	Mixed	78.8§	NR	4.3‖	NR	Follow-up 2-12 mo: 2 patients with shunt, 1 with normal Pa_{O_2} within a few weeks
Stoller et al, 1990[11]	1	39	Primary biliary cirrhosis	62	290	18	NR	Normal shunt fraction (5.1%) at 37 days
Dimand et al, 1991[14]	3	13-53	Not specified	50.3§	289§	NR	Present	Decreased shunt and off supplemental O_2 at 3-4 mo
Levin et al, 1991[13]	1	11	Biliary atresia	44.8	NR	NR	Large	6 mo: resolution of shunt; 8 mo: improvement in O_2 saturation
McCloskey et al, 1991[17]	1	17	Cryptogenic cirrhosis	41	115	NR	30	9 mo: Pa_{O_2} 79 mm of mercury and 3% shunt
LaBerge et al, 1992[15]	2	12, 14	Biliary atresia	52§	233§	35	Present	Improved exercise tolerance at 3 mo, normal shunt study at 5 mo
Barry et al, 1993[20]	7	NR	Mixed	NR	NR	24.5	NR	Follow-up interval 3-18 mo: shunt fraction improved by 14% as a group
Itasaka et al, 1993[18]	1	13	Cryptogenic cirrhosis	42	417	52¶	48	Resolution of shunt at 165 days after transplantation
Schwarzenberg et al, 1993[19]	1	18	α_1-Antitrypsin deficiency	34	57	NR	Large	At 14 mo: Pa_{O_2} 116 mm of mercury and no shunt
Scott et al, 1993[16]	6	NR	Not specified	35-71#	350-460#	NR	12-19	3 patients: prompt resolution of shunts; 3 patients: long postoperative course, but shunt resolved

NR = not reported

*The values are the calculated shunt fraction with the patient breathing 100% oxygen, unless otherwise stated.
†Technetium Tc 99m-labeled macroaggregated albumin scan.
‡The numbers represent saturation values.
§The number is the mean value.
‖Multiple inert gas elimination technique was used.
¶By direct measurement of the shunt at cardiac catheterization.
#The numbers represent the range.

likely. Similarly, the timing of posttransplantation retesting for the hepatopulmonary syndrome was not uniform, so that our understanding of the frequency of reversal of the syndrome and of the time frame over which reversal occurs is incomplete. Finally, the small number of patients having the reversal of the hepatopulmonary syndrome in this and other series precludes a clear understanding of pretransplantation clinical features associated with the reversibility of the syndrome. Indeed, in the absence of a better understanding about predicting reversibility of the syndrome, a firm recommendation to do transplantation in all patients with the hepatopulmonary syndrome is not possible. Nonetheless, bolstered by the observation that the syndrome can reverse following liver transplantation, it is reasonable to consider this procedure for patients whose hepatopulmonary syndrome is the major debilitating feature[11] and who are otherwise deemed to be candidates for liver transplantation. To address the aforementioned shortcomings, we are currently prospectively evaluating liver transplantation candidates referred to our institution, in which patients are routinely assessed for the hepatopulmonary syndrome as part of their pretransplantation evaluation.

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Articles

Cuba's National AIDS Program
The First Decade

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There is a high incidence of infection with the human immunodeficiency virus (HIV) in many Caribbean nations. But by 1993 Cuba, with a population of greater than 10 million people, had fewer than 1,000 seropositive persons and less than 200 cases of the acquired immunodeficiency syndrome (AIDS). To investigate Cuba's approach to the AIDS epidemic, we visited Cuba, reviewed published statistics, spoke with health care officials, interviewed HIV-positive patients, and toured medical facilities. Cuba established an extensive HIV surveillance program in 1983, and more than 15 million HIV antibody tests have been done. The sexual contacts of all infected persons are closely observed. A national education program is evolving. Since 1986, all known HIV-positive patients have been placed in sanitariums, which is the most controversial aspect of Cuba's program. We review available information on AIDS in Cuba and describe that nation's attempt to prevent the spread of disease. We discuss how the political system and Cuba's relative isolation have influenced this approach. Strategies have been developed that may be of limited efficacy and would not be acceptable in most Western nations.

(Granich R, Jacobs B, Mermin J, Pont A: Cuba's national AIDS program—The first decade. West J Med 1995; 163: 139-144)

The World Health Organization (WHO) estimates that worldwide between 9 and 12 million people are infected with the human immunodeficiency virus (HIV).[1(pp886-887)] As of January 1, 1992, more than 300,000 people were infected with HIV in the Caribbean countries.[1] About 8,000 cases of the acquired immunodeficiency syndrome (AIDS) from that region have been reported to the WHO (Table 1).[2] Although HIV infection has been a major problem for many countries in the Caribbean, as of May 1993, Cuba with a population of more than 10 million, has had only 187 cases of AIDS.

To investigate Cuba's approach to preventing the spread of HIV, we obtained a research grant from the Center for Latin American Studies at Stanford (California) University. In May 1993, two of us (R.G. and B.J.), both fluent in Spanish and English, spent three weeks in Cuba. To gather data that were as objective as possible, we elected not to travel as official guests of the government. Cuban health care professionals who were directly involved in AIDS care were open to meeting with us.* We talked with policy makers, visited health care facilities, interviewed 15 persons with HIV infection, and polled many residents of Havana. We describe our impression of Cuba's current strategy to confront the AIDS epidemic. We were not involved in primary data collection. The accuracy of the data presented is difficult to assess, but because little information regarding HIV infection in Cuba has been published, this article provides an opportunity to critically examine the available information.

Cuban Health Care System

Cuba's approach to the HIV epidemic is an integral component of its national health care system. It has been well documented that Cuba's national health statistics resemble those of an industrialized country.[3-6] The infant birth and mortality rates are low. Infectious diseases that are related to poor sanitary conditions are uncommon. The incidence of cancer and of cardiovascular disease is similar to that of the United States, and there is an aggressive tuberculosis control program.[7] The prevalence of injection drug use is extremely low. A recent epidemic of optic and peripheral neuropathy affecting thousands

*Interviews in Spanish and English were held with the following persons: Jorge Perez, MD, Director, Santiago de las Vegas sanatorium, and Professor of Pharmacology and Medicine, Havana University Medical School; Giselda Sanabria, MD, Director of the National Center Health Education; Lourdes Flores, MD, Director of the National Center for Sex Education; Juan Carlos de la Concepcion, MD, Director, Grupo Prevención SIDA, and resident of Santiago de las Vegas sanatorium, Havana; Raul Llanos, PhD, economist and resident of Santiago de las Vegas sanatorium; Jeremias Ojito, MD, Director, National Center for Medical Science Information of the Ministry of Public Health; Cosme Ordones, MD, Director of Policlinic, Plaza de la Revolución, Havana, and Founder of the National Family Medicine Doctor Program; Sergio Sokol, MD, Family Medicine Clinic physician, Consultorio #21, Plaza de la Revolución; and Karen Wald, Journalist. We also visited the Santiago de las Vegas sanatorium in Havana, the Pedro Kouri Tropical Medicine Institute AIDS ward and reference laboratories, the Plaza de la Revolución Policlinic, a Family Doctor Clinic, the National Center for Medical Science Information, the National Center for Health Education, the National Center for Sex Education, and the National Center for the Perfection of Medical Personnel.

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ABBREVIATIONS USED IN TEXT

AIDS [SIDA]= acquired immunodeficiency syndrome
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
WHO = World Health Organization

of persons has been reported, and some foreign and Cuban investigators have concluded that the outbreak may be the consequence of nutritional deficiencies related to worsening economic conditions.[8,9]

Health care delivery is based on a network of 420 *policlinics* (large multispecialty clinics) with large referral hospitals in each province. This system is modeled after similar approaches in eastern European countries. In 1983 the Family Doctor Program was initiated to deliver community-based primary care. Family physicians maintain *consultorios* (offices), and each is responsible for the health of 600 to 1,000 residents. They regularly review their case load with specialists and other health care professionals. House calls are a key component of the program, and family physicians have personal relationships with many of their patients. They routinely identify persons at risk for HIV infection and provide AIDS education and screening.

Cuba's Current HIV Screening Strategy

The Cuban government established a national AIDS program in 1983. The importation of blood products was prohibited, and a domestic acquisition program was instituted. Annually there are more than 600,000 blood donations, each of which is tested for HIV. In 1984 a surveillance system was implemented in hospitals and clinics to detect possible defining diseases of HIV such as Kaposi's sarcoma and *Pneumocystis carinii* pneumonia.

In 1986 HIV screening was initiated for all people who had traveled since 1976 to countries that had reported cases of HIV infection. Since 1987 screening has been done systematically for defined groups, including patients admitted to a hospital, patients with sexually transmitted diseases and their partners, Cubans traveling outside the country, pregnant women in the first trimester and at delivery, prison inmates, workers in the tourist industry, merchant sailors, and public health employees. As of May 1988, 32,750 temporary residents had been tested on arrival and six months later. Testing for HIV has been integrated into routine health care, and many Cubans now perceive the HIV test as part of a normal health screening. About 2 million tests are performed annually.

In 1986 Cuba began the development of a domestic enzyme-linked immunosorbent assay (ELISA) and a Western blot test for HIV. A national network of 52 laboratories now does initial serologic screening with domestically manufactured tests. Specimens that are ELISA-reactive are retested and, if positive on a second test, are referred to the National Reference Laboratory. The reference laboratory repeats the test using competitive and indirect ELISA systems and also runs a Western blot test. Patients with a positive result are required to provide a second serum specimen. If the patient continues to test positive, the National Division of Epidemiology is notified. Indeterminate results are followed up with a radioimmunoprecipitation test and viral culture. World Health Organization criteria are used to interpret test results.[10,11] According to Ministry of Public Health officials, Cuba's tests have been validated with an international standard in collaboration with the Oswaldo Cruz Foundation in Brazil and Sweden's Ministry of Public Health.[12,13]

TABLE 1.—*Comparative AIDS Statistics in Caribbean Basin as of January 1, 1992*

County/Territory	AIDS Cases, No.*	Population, millions†	AIDS Cases/ 100,000
Barbados	250	0.3	83
Dominican Republic	1,574	7.5	21
Haiti	3,000	6.4	47
Puerto Rico	8,000	3.5	229
Cuba	95	10.5	1

AIDS = acquired immunodeficiency syndrome

*From the World Health Organization.[2]

†From the 1992 World Population Data Sheet, Population Reference Bureau, Inc, Washington, DC, Information.

Results of the Screening Program

Between April 1986 and May 1993, about 15 million ELISA tests were performed with Western blot test confirmation of 927 people with HIV (some persons were screened more than once); 71% were male. Of the male cases, 62% were homosexual or bisexual. Of the 927 cases, 54% were attributed to heterosexual transmission. No case of HIV transmission could be ascribed to injection drug use. With about 180,000 births annually, there have been only 4 pediatric cases of HIV infection. Less than 2% of HIV cases were considered related to occupational exposure or perinatal or blood product transmission. During this seven-year period, there were 3,728,689 blood donations, of which 51 (0.001%) were HIV-positive. Most of the cases of HIV-1 infection occurred in the urban province that includes the capital, Havana. In all, 79% of patients report acquiring HIV in Cuba, and 18% were infected in Africa. The remaining cases resulted from acquisition in the Americas or Europe. Screening of inpatients, pregnant women, sexual contacts of people seropositive for HIV, and patients with sexually transmitted disease has demonstrated HIV seroprevalence rates of 0.003%, 0.000016%, 6.8%, and 0.013%, respectively.

Figures 1 and 2 show the annual incidence of HIV and AIDS from 1986 through 1992, but the incidence of HIV remains low. The number of AIDS cases, although small, is rising. This increase probably reflects disease progression in people infected in the early 1980s. Of persons who test positive for HIV, 63% were detected in an early phase II or III of the 1987 revised Centers for Disease Control and WHO AIDS classification.[11,13] The mean survival with AIDS is 18 months. The principal opportunistic infections among the first 125 AIDS patients are similar to those found in industrialized countries, with the exception that there is a paucity of cases of tuberculosis (Table 2).

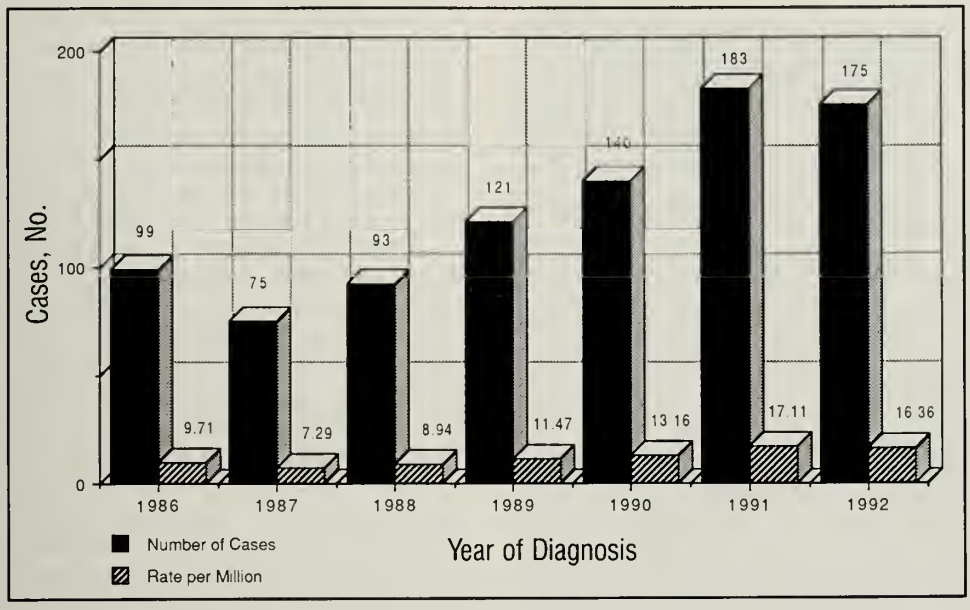

Figure 1.—Both the number of new cases of infection with the human immunodeficiency virus (HIV) and the rate per million rose relatively steadily between 1987 and 1992. The increased number of cases noted in 1986 is due to the introduction of HIV testing to Cuba during that year. People who were infected before and during 1986 were included; subsequent years better reflect the incidence of new infections.

Approach to Patients Positive for the Human Immunodeficiency Virus

People with confirmed positive tests are contacted and counseled by an epidemiologist or family physician. The patient is then referred to the National Institute of Tropical Medicine for evaluation and placement in a sanitarium. Pregnant women who are HIV-positive are counseled and given the option to have a therapeutic abortion. Abortions are strongly recommended, and about 98% of HIV-seropositive mothers have elected to terminate their pregnancies. Future plans call for a team of health care workers headed by a person with HIV to contact and counsel people who are newly diagnosed with HIV.

In 1986 the tracing of contacts and the screening of sexual partners of HIV-positive persons was begun. Sexual contacts are tested for HIV every three months for a period of one year after the last sexual contact with the

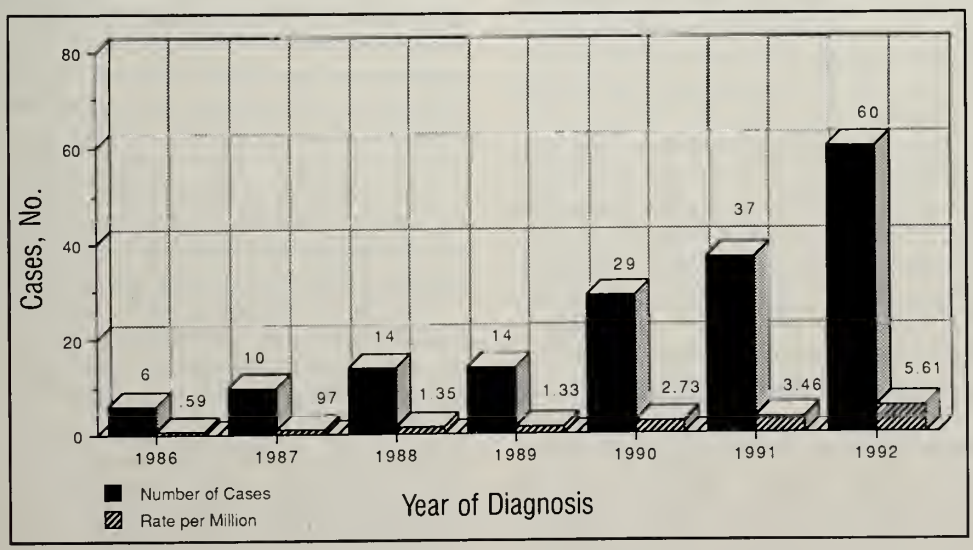

Figure 2.—Both the number of new cases of the acquired immunodeficiency syndrome (AIDS) and the rate per million rose relatively steadily between 1986 and 1992. Any effects of a human immunodeficiency virus control program would not be reflected by a changing incidence of AIDS for several years due to the long incubation period of the virus.

TABLE 2.—*Opportunistic Infections and Malignant Neoplasms in 125 Cuban Patients With the Acquired Immunodeficiency Syndrome (AIDS)**

Diagnosis	AIDS Patients %	AIDS Patients No.
Pneumocystis carinii pneumonia	50	63
Oral candidiasis	27	34
Hairy leukoplakia	17	22
Cryptosporidiosis	17	21
Toxoplasmosis†	15	19
Disseminated cytomegalovirus	11	14
HIV wasting syndrome	10	12
Herpes simplex virus (mucocutaneous)	9	11
Lymphoma	6	8
Cryptococcus species infection	4	5
Kaposi's sarcoma	4	5
Histoplasmosis	4	5

HIV= human immunodeficiency syndrome

*From written communication, Jorge Perez, MD, Director, Santiago de las Vegas sanitorium, May 1993.
†Central nervous system.

proband. Sexual partners are observed for as long as they remain in contact with the index case. By 1989 approximately 80% of the 1,317 sexual contacts of HIV-seropositive persons had been tested. Of these, 5.1% of the partners of male homosexuals, 10.4% of the partners of male heterosexuals, and 3.4% of the women partners of male bisexuals were infected.

Sanitarium Treatment Program

The most controversial aspect of the national AIDS program is the use of sanitariums for people with HIV. Cuba's sanitarium policy was established in 1986 and has evolved over time. The Santiago de las Vegas sanatorium was constructed by the military to house patients with HIV in an attempt to reduce transmission of the disease. The first residents were predominantly returning "internationalists" who had served in Africa. In 1987 a growing number of civilians were found to be HIV-seropositive, and the military handed over responsibility for the center to the Ministry of Public Health, who transformed the barracks into a sanitarium facility. The sanitarium is now an enclosed suburban community of several acres that includes houses, apartments, a dormitory, a library, recreational facilities, a clinic, and an infirmary. The quality of the housing has improved and meets or exceeds current Cuban housing standards. Sanitarium residents are provided with free housing, food, and medical care. They are given their former salaries and have the option to work.

Persons with newly diagnosed HIV infection are placed in 1 of the 14 provincial sanitariums nearest their homes. Residents undergo evaluation to assess the risk that they might transmit HIV while in the community. Most residents receive a satisfactory evaluation and are permitted to leave the sanitarium for short periods of time without a chaperone. Residents with "unsatisfactory" evaluations are allowed to leave only with a chaperone. These persons are considered to be at risk for transmitting HIV or unable to care for themselves. Evaluations are frequent, and changes in status are not uncommon.

The sanitarium policy regarding contact between residents and the community has evolved. During phase I, which began in 1986 and lasted for three months, patients were removed from their communities, placed in a sanitarium, and prohibited from leaving the premises, although visitors were allowed. Under phase II, patients were permitted to leave for 18 hours four times every three months only if accompanied by a chaperone. During phase III, which began in 1989, some patients are permitted to go out without chaperones. The frequency and duration of leave have also increased over time. Currently patients are permitted to depart Friday morning and return Monday evening. Additional passes during the week are granted routinely to many patients. Phase IV is scheduled for implementation, and this new policy includes a transition to a sanitarium-based ambulatory care program. Most residents would be permitted to voluntarily return to their communities after an initial evaluation and treatment period.

Cuban officials feel pressure from many sources about their sanitarium policy. These include residents and their families, Cuban dissidents, international publicity, and new epidemiologic information regarding the modes of HIV transmission.[14]

Sanitarium residents are observed by a team of physicians, psychologists, social workers, and nurses. The level of knowledge of the health care professionals, the availability of medications, and the nutritional support provided to residents exceed the Cuban national standard. There is 1 physician for every 50 patients, and health care workers frequently visit the dwellings of residents. An infirmary is accessible on a 24-hour basis. Immunologic status is evaluated using CD4+ counts and standard clinical measures such as signs of opportunistic infections. Common antibiotics, antifungals such as fluconazole and amphotericin B, antiretrovirals such as zidovudine and didanosine, and antivirals such as ganciclovir and acyclovir are usually available. Herbal remedies are also used. Patients with serious complications are referred to the National Tropical Medicine Institute. Cuba's worsening economic situation and the trade embargo by many western nations is reducing the availability of medicines, equipment, medical literature, and some basic supplies.

Interviews with sanitarium residents revealed a variety of opinions. They appreciated the high standard of care and the living conditions. They almost universally expressed frustration with the restriction of freedom. Given the choice, some residents would not accept the sanitarium system. They questioned the possible benefits to them or the community. For others, however, sacrifice for the community is an integral part of the postrevolutionary Cuban society. Therefore, the curtailment of individual liberty and privacy is perceived by some as necessary to maintain adequate public health and safety.

Life in Cuba outside the sanitariums is difficult, as there are shortages of food, housing, electricity, and trans-

portation. Some residents had mixed feelings as to whether they would want to leave the sanitarium once phase IV is implemented. They weighed the benefits of adequate medical treatment, housing, peer support, and ample nutrition against the restrictions on freedom and the separation from their former community.

Educational Campaign

Some authors have criticized Cuba's lack of effort in AIDS education compared with its approach to screening and treatment.[12,15] Before 1989, Cuban AIDS education relied on European advertisements that were culturally foreign to most Cubans. Alternatively, they featured formally attired Cuban health professionals conversing in complicated medical terms. Recently several culturally specific education projects have been developed. In 1990 the Grupo Prevención SIDA [AIDS], comprising HIV-seropositive physicians, economists, psychologists, and laborers, collaborated with the National Center for Health Education to establish an information center in downtown Havana. Grupo Prevención SIDA also initiated street and university AIDS outreach programs. High-risk groups, such as "*rockeros*"—young people who are interested in rock music and who lead an "alternative" lifestyle—have been targeted by a newly formed multidisciplinary AIDS education consortium. A bimonthly two-hour radio program has been started that features music, interviews, and conversations with people who are HIV-positive.

In 1993 Grupo Prevención SIDA, many of whose members were residents in the sanitariums, was promoted to the status of a national commission charged with setting HIV educational policy and implementing national programs. Emphasis is placed on careful partner selection, safer sex practices, barrier use, and decreasing the number of sexual partners. Information on AIDS is now presented on television daily. The interviews we conducted with people in Havana consistently showed a high level of HIV awareness. There seemed to be an impressive knowledge of the modes of transmission and the demographics of the disease. Interviewees felt that the HIV prevalence was low and thought that all people with HIV were in sanitariums.

Economic Costs of Cuba's HIV Program

A total of 12% of the Cuban national budget is devoted to health care (Cosme Ordones, MD, written communication, May 1993). Expenditures for HIV-related issues have been estimated at $15 to $20 million (in US dollars) annually. The initial screening campaign required $1.7 million to purchase 42 spectrophotometers, 750,000 diagnostic tests, and laboratory materials. A total of $3 million was invested in the development of the Cuban ELISA and Western blot test. Tests now cost 22 cents each. The cost of maintaining a resident in a sanitarium is about $15,000 per year. These figures represent an estimate of some of the more obvious dollar costs required to implement and maintain the program. Further research is needed to analyze the full economic effects of the AIDS program.

Discussion

Cuba's National AIDS program is of particular interest because of its aggressive strategy to prevent the spread of HIV. Serious ethical questions exist regarding the restrictions placed on people with HIV. The current political reality of Cuba and its relationship with the United States can make it difficult for independent sources to collect accurate information. Therefore, some have questioned the validity of reports regarding the epidemiology of HIV in Cuba.[16-18] Although only limited outside research has been done, several investigators are convinced of the accuracy of HIV-related and other health care data.[12,19-21] During our three-week stay, we were impressed by our easy access to information. Although we cannot be absolutely certain, we think that the data that were given to us and that are presented in this article are accurate.

Over the past seven years, Cuba may have completed the most comprehensive national HIV serologic study in the world. It is unclear whether the HIV screening campaign has been an important factor in preventing the spread of HIV, but it is impressive that 55% of the people detected with HIV are asymptomatic. Of interest, there have been few documented occurrences of blood-borne or perinatal HIV transmission.

Cuba's well-developed public health system works to the advantage of the AIDS prevention program. Advances in health care are heavily promoted by the government and are often linked to revolutionary goals. In this context, screening for HIV may now be viewed as a routine part of a comprehensive medical examination. Since the revolution, there has been an aggressive public health response to communicable diseases such as tuberculosis. Strong government emphasis is placed on tuberculosis diagnosis, contact screening, and supervised chemotherapy at a primary care level. There are no known cases of tuberculosis among people with HIV. This may be due to the low incidence of tuberculosis in Cuba and the fact that people with HIV are relatively isolated and receive frequent medical attention.

The AIDS program relies on contact tracing. In addition to testing sexual partners, health workers also teach them about HIV transmission. In a country with an organized health care system, limited resources, low HIV prevalence, and a societal commitment to caring for those infected, contact tracing may provide an efficient method for HIV control. Although some persons who perceive themselves at risk for HIV infection may attempt to avoid contact with the health care system, Cuba's reliance on neighborhood physicians, its strong community organizations, and the lack of an underground drug culture may make it difficult to evade HIV screening. Cuba's economic crisis and the growth of prostitution and tourism may have serious adverse effects on AIDS prevention efforts.

The most controversial aspect of the AIDS program is the sanitarium policy. Criticism has focused on the efficacy and ethics of this abridgment of personal freedom.[14-18] Although restrictions on persons in the

sanitariums are lessening with time, they remain unacceptable to many people both inside and outside of Cuba. Cuba's response to the HIV epidemic may be better understood in the context of its social structure. Cuba is organized along greatly different principles from those found in many other countries. The interests of the state and community are placed before individual concerns. Residents of Havana with whom we spoke frequently expressed the view that collective well-being takes precedence over individual rights. In this context, because medical care and social support are guaranteed for all people diagnosed with HIV, and because the sanitarium system is perceived as being in the public interest, massive HIV screening and the use of sanitariums may be acceptable to most Cubans. It is questionable whether the use of sanitariums has played a major role in thwarting the spread of HIV in Cuba. Future studies and scientific exchanges may help clarify the contributions of factors such as the sanitarium system, Cuba's relative isolation, and the extensive screening program on the low incidence of disease.

Although some lessons may be learned from Cuba's comprehensive and coordinated response to HIV, many aspects of Cuba's policy are not acceptable or applicable in other countries. In many nations, the prevalence of HIV infection is much greater. The use of injection drugs is a compounding problem. Most societies would be unwilling or unable to impose widespread HIV screening on its citizens. Even if it could be demonstrated that the sanitarium policy has been efficacious, it is improbable that the restrictions to freedom of a sanitarium system would be acceptable in 1995. In countries with a large number of infected persons, there may be neither the consensus nor adequate public resources to provide economic support, housing, and health care for all people with HIV.

Restrictions on travel render scientific exchange between Cuba and other nations difficult. In the face of the global HIV pandemic, it is imperative to share knowledge regarding HIV epidemiology and all strategies that might prevent the spread of the virus.

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Conferences and Reviews

Anticoagulation and Atrial Fibrillation

Putting the Results of Clinical Trials Into Practice

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Dawn E. DeWitt, MD, Chief Medical Resident, Henry Rosen, MD, Professor and Associate Chair, and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

The thromboembolic risk of atrial fibrillation varies with the underlying cause, associated heart disease, and history of previous embolism. Decisions regarding warfarin anticoagulation therapy require a careful assessment of relative risks of thromboembolism and bleeding. Anticoagulation is strongly indicated for valvular atrial fibrillation and to prevent recurrent stroke in patients with atrial fibrillation and previous stroke or transient ischemic attack. Several randomized trials have consistently shown a reduction of the risk with the use of warfarin in nonvalvular atrial fibrillation, and anticoagulation is recommended. With a careful selection of patients, the risk of major bleeding on warfarin therapy is 2% to 4% per year. Aspirin therapy is less efficacious but also less risky than warfarin. Patients younger than 60 with lone atrial fibrillation do not require anticoagulation.

(Wipf JE: Anticoagulation and atrial fibrillation—Putting the results of clinical trials into practice. West J Med 1995; 163:145-152)

Case Summary

The patient is a 74-year-old man with a history of diabetes mellitus, hypertension, and congestive heart failure in whom chronic atrial fibrillation developed. After anticoagulation, he was admitted for elective cardioversion. On examination, he was without murmur or congestive heart failure. An electrocardiogram showed atrial fibrillation and an old, silent, anterior-wall myocardial infarction. By echocardiography, the left atrial size was 4.8 cm, and no valvular disease or thrombi were seen. The patient did not convert to sinus rhythm with the administration of quinidine sulfate, and frequent ventricular pauses developed, requiring discontinuation of the drug. Electrocardioversion was not attempted. Ongoing warfarin sodium anticoagulation was continued. Four months later, the patient was admitted with an embolus of the right iliac artery. At this time, a prothrombin time (PT) international normalized ratio (INR) was subtherapeutic at 1.4.

Problems

This case poses a number of challenging questions in the management of atrial fibrillation and the prevention of thromboembolic complications. Addressing the following should help to clarify therapy:

- What is the cause of atrial fibrillation?
- What is the risk of thromboembolism, especially to the brain?
- Can the risk of thromboembolism be reduced by warfarin therapy?
- How great is the risk of hemorrhage on warfarin therapy?
- Is the use of aspirin a reasonable alternative?

Many physicians have faced similar questions with other patients. Like this clinical case, many cases have unique elements that make management difficult. Although it may be tempting to defer complex management decisions to cardiologists or neurologists, primary physicians are often best able to assess patients' level of cognitive and physical function and suitability for anticoagulation. Because long-term anticoagulation therapy is frequently managed by primary care providers, familiarity with indications for the use of warfarin in patients with atrial fibrillation allows clinicians to be actively involved in decisions to initiate and maintain anticoagulation therapy.*

*See also the editorial by S. R. Stratton, MD, "Warfarin Sodium or Aspirin Therapy to Prevent Stroke in Nonrheumatic Atrial Fibrillation," on pages 177-179 of this issue.

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ABBREVIATIONS USED IN TEXT

AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation Study of Copenhagen
BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA = Canadian Atrial Fibrillation Anticoagulation [study]
INR = international normalized ratio
ISI = international sensitivity index
PT = prothrombin time
PTR = prothrombin time ratio
SPAF I, II = Stroke Prevention in Atrial Fibrillation [studies] I and II
SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation [study]

Factors That Predispose to Atrial Fibrillation

The most prevalent cause of atrial fibrillation has historically been rheumatic valvular heart disease, predominantly mitral stenosis. The connection between atrial fibrillation and mitral valve disease was first made in the 1700s by Jean Baptiste de Senac (1693 to 1770), physician to King Louis XV, who published the first text on cardiology.[1] He correlated an irregular pulse and palpitations with autopsy observations of mitral valve disease. At the turn of the 20th century, Sir James Mackenzie found that the a wave of the jugular pulse was caused by atrial contraction and therefore was lost in atrial fibrillation.[2]

In the United States, where rheumatic heart disease is uncommon, the cause of atrial fibrillation is usually nonvalvular heart disease, principally atherosclerotic cardiovascular disease. The patient in the case reviewed here has typical nonvalvular atrial fibrillation with congestive heart failure, coronary artery disease, and hypertension. The prevalence of various conditions in atrial fibrillation and the prevalence of atrial fibrillation in each condition are shown in Table 1.[3] The prevalence of atrial fibrillation is low in patients with angina, but about 10% of patients will have it transiently after coronary artery bypass grafting or myocardial infarction. It is present in nearly half of patients with mitral stenosis and 75% of patients with mitral regurgitation requiring valve replacement. Isolated aortic valve disease is associated with atrial fibrillation in only 1% of cases.[4] It is infrequent in cases of acute pericarditis, but common in chronic pericardial constriction. Of patients with thyrotoxicosis, 10% to 20% have atrial fibrillation, and a third will have persistence of their arrhythmia after the treatment of hyperthyroidism.

Atrial Fibrillation and Thromboembolism

Atrial fibrillation is currently the cause of nearly half of cardiogenic embolic events.[5,6] An estimated 2% to 4% of adults, or 1.5 to 2 million Americans, have atrial fibrillation, with a great effect on the incidence of stroke. Of patients presenting with acute stroke, 15% to 25% are in atrial fibrillation.

Emboli of cardiac origin are less commonly associated with rheumatic heart disease, acute myocardial infarction, or prosthetic valves. Most clinically recognized cardiac emboli are cerebral, with only a third at systemic sites, such as the extremities, as in the patient presented here. The kidneys and the spleen are also relatively common sites of embolism.

Thrombi as small as 3 to 4 mm are reported to cause strokes. Because a quarter of strokes in patients with atrial fibrillation are nonembolic, there may be other mechanisms by which thrombi cause stroke.

Confirming the clinical diagnosis of cardioembolic stroke is difficult. There are no universally agreed-on criteria, and individual features are neither sensitive nor specific. Suggestive features that distinguish a stroke due to cardiogenic emboli from a carotid artery source include the knowledge of a possible cardiogenic source, a maximal deficit at its onset, a large infarct, or infarcts occurring in more than one vascular distribution.[6] Hemorrhagic transformation may be seen in patients with embolic strokes following reperfusion of the stroke area after breakup of the embolism. The presence of a cardiogenic source in the absence of cerebrovascular disease is most suggestive of the diagnosis.

The risk of thromboembolic events, most of which are strokes, is known from several epidemiologic studies of atrial fibrillation. The Framingham Heart Study, which monitored 5,200 residents of Framingham, Massachusetts, for the development of cardiovascular disease, found a high risk of stroke in those with valvular atrial fibrillation, 17.6 times greater than in controls, with the patients' mean age being 60 years.[7] The risk of stroke in patients with nonvalvular atrial fibrillation, with a mean age of 70 years, was 5% per year, or 5.6-fold higher than in controls. The increased incidence of thromboembolism

TABLE 1.—*Diseases Associated With Atrial Fibrillation**

Disease	*Prevalence in Patients With Atrial Fibrillation, %*	*Prevalence of Atrial Fibrillation in Each Disease, %*
Valvular heart disease		
Rheumatic valvular disease	20-30	20
Nonvalvular heart disease		
Coronary artery disease	50-60	1
Hypertension	40-60	5-10
Acute myocardial infarction	<5	5-15
After coronary bypass surgery (transient)	<5	30-40
Congestive cardiomyopathy	<1	20
Hypertrophic cardiomyopathy	<1	10
Acute pericarditis	<1	5
Pericardial constriction	<1	35
Alcohol (holiday heart syndrome)	<1	40
Conductive system disease (sick sinus syndrome, Wolff-Parkinson-White syndrome)	<5	<5
Hyperthyroidism	2.5	20-30
Lone atrial fibrillation	10	--
Pulmonary embolism	<1	3

*Modified from Albers et al,[3] with permission from the *Annals of Internal Medicine*.

in nonvalvular atrial fibrillation has been confirmed in other studies, with rates five to seven times those in controls.[8,9] Clearly underlying cardiovascular disease is an important factor in determining the risk of stroke from atrial fibrillation.

Trials of Anticoagulation in Nonvalvular Atrial Fibrillation

Several recently reported randomized trials of anticoagulation in nonvalvular atrial fibrillation show the efficacy of using warfarin.[10-15] To interpret the anticoagulation intensity of each trial and compare studies of warfarin bleeding risk, the relationship between the prothrombin time ratio (PTR) and the INR must be understood. The PTR is a patient's PT over the PT from batched controls. The INR is derived from the PTR on a specially designed nomogram for a given international sensitivity index (ISI), which is provided by the manufacturer for each shipment of thromboplastin reagent and varies in different laboratories. For example, an INR range of 2.0 to 3.0 corresponds to a PTR range of 1.5 to 1.8 when the ISI is 1.8 and a PTR of 1.4 to 1.6 when the ISI is 2.3.[16] The INR is not more accurate than the PTR as it is derived from the PTR, but the INR allows a comparison of prothrombin times from different laboratories. In the Northwest, about 70% of clinical laboratories use the INR measurement, compared with 50% or less across the country.

The published randomized trials in nonvalvular atrial fibrillation are the Atrial Fibrillation, Aspirin, Anticoagulation study (AFASAK), reported in 1989 from Copenhagen; the Stroke Prevention in Atrial Fibrillation studies (SPAF I and II) and the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), which are multicenter American trials; the Canadian Atrial Fibrillation Anticoagulation study (CAFA), a multicenter Canadian trial; and the Stroke Prevention in Nonrheumatic Atrial Fibrillation study (SPINAF), a Veterans Affairs cooperative trial.[10-15] In all, about 3,000 patients were enrolled in these trials.

One of the problems in generalizing results from the trials to clinical practice is that more than 90% of screened patients were excluded from the studies. Enrolled patients included elderly patients (older than 75), persons with either sustained or intermittent atrial fibrillation, and those with atrial fibrillation of long duration or of recent onset. Left atrial size was not a criterion for enrollment. Criteria for patient exclusion included, but were not limited to, mitral stenosis, a requirement or contraindication for either warfarin or aspirin therapy, high bleeding risk, recent stroke, recent transient ischemic attack, or the presence of emboli. Risk factors for bleeding that resulted in a patient's exclusion were active peptic ulcer, bleeding disorder, previous hemorrhage, occult bleeding, uncontrolled hypertension, severe renal or hepatic disease, dementia, gait disorder, and alcoholism.

The highest intensities of anticoagulation were in the AFASAK and SPAF studies, with INR ranges of 2.8 to 4.2 and 2.0 to 4.5, respectively. The other trials more closely approximated an INR range of 2.0 to 3.0 currently recommended for atrial fibrillation. Two trials had a randomized arm of aspirin therapy—AFASAK, with a dose of 75 mg aspirin per day, and SPAF, 325 mg of aspirin per day. (SPAF II was a continuation of SPAF I after the placebo arm was dropped, and those patients were randomly reassigned to receive aspirin, 325 mg, or warfarin.) Patients in the control arm of the BAATAF trial were allowed to take aspirin, and 46% took aspirin regularly, most at 325 mg per day. The aspirin data are discussed in detail later.

The incidence of central nervous system events in patients treated with warfarin and in controls taking a placebo on an intention-to-treat analysis is graphed in Figure 1.[10-14] Transient ischemic attacks are excluded, and all stroke events had a persistence of neurologic deficits of longer than 24 hours. All five trials consistently showed a similar magnitude of benefit of using warfarin over placebo, for an overall significant stroke risk reduction of 70%. In the AFASAK study, all but one of the stroke events occurred in patients with subtherapeutic INR values. All trials were stopped prematurely when an interim analysis showed substantial warfarin benefit, or in the case of CAFA, a trend toward warfarin benefit and the other trial results were known. The annual incidence of noncerebral systemic emboli was also reduced by warfarin therapy in each trial. The overall reduction in the incidence of systemic thromboembolism was 81%, statistically insignificant because so few events occurred overall.[17,18]

Bleeding Complications of Warfarin Therapy

Warfarin sodium therapy is highly efficacious in reducing stroke in patients with atrial fibrillation, but it carries a hemorrhagic risk. Each trial had a different definition of major bleeding, but events included were se-

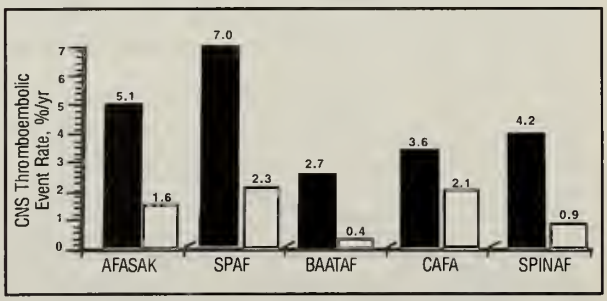

Figure 1.—The efficacy of the use of warfarin sodium is compared with that of placebo control in 5 prospective, randomized trials of nonvalvular atrial fibrillation. The annual incidence of central nervous system (CNS) events, excluding transient ischemia attacks, is shown for control (**dark bars**) and warfarin (**light bars**) arms of each study. AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation study of Copenhagen; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation study; CAFA = Canadian Atrial Fibrillation Anticoagulation study; SPAF = Stroke Prevention in Atrial Fibrillation study; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation study

vere and often life-threatening. For example, major bleeding in the BAATAF study was defined as intracerebral, fatal, or requiring transfusion of four or more units of blood products within 48 hours.[12] The rates of major bleeding in the nonvalvular atrial fibrillation trials were low, all 1.5% or less per year, with the exception of SPAF. The other trials had annual rates of 0.8% to 1.5% and 0.3% to 0.9% in the warfarin and placebo arms, respectively. In SPAF I, the trial with the highest INR intensity range, major hemorrhage occurred in 1.5% per year of those on warfarin therapy and 1.6% per year of those on placebo or aspirin therapy. The SPAF II trial had annual rates of 4.2% and 1.6% per year for patients on warfarin and aspirin therapy, respectively, in patients older than 75. How do these rates of bleeding compare with data on warfarin anticoagulation in unselected patients?

A recent multicenter study determined bleeding rates in 928 "unselected" consecutive patients observed in an anticoagulation clinic (distinct from trials just reviewed) (Figure 2).[19] The mean age at the start of the study was 57 years. Serious bleeding was defined as any bleeding that prompted a workup, such as cystoscopy, or that required no more than two units of blood transfused. Life-threatening bleeding included that leading to irreversible sequelae, cardiopulmonary arrest, surgical intervention or angiography, hypotension, transfusion of at least three units, or a hematocrit of 0.20 (20%) or less. Fatal bleeding was defined as that leading directly to a patient's death.

The cumulative incidence of serious bleeding was high, and bleeding occurred in 12% of patients during the first year of anticoagulation. After eight years, 40% of patients had had at least one episode of serious bleeding. The risk of life-threatening or intracranial bleeding was low, however, being 1.6% per year, and fatal bleeding occurred in four patients (0.4%), corresponding to the bleeding rates in the randomized atrial fibrillation trials. These rates are also comparable to several other recent studies of warfarin anticoagulation intensity in an INR range of 2 to 3. In a carefully selected group with close monitoring, life-threatening and fatal bleeding events are uncommon. Earlier studies reporting major bleeding rates as high as 10% to 15% per year used greater intensities of anticoagulation and included agents other than warfarin.[20]

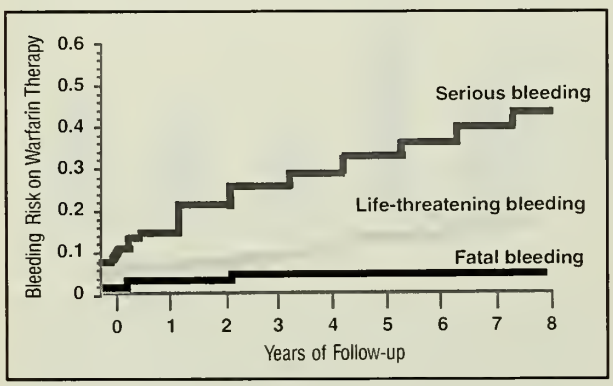

Figure 2.—In 928 unselected, consecutive patients on warfarin therapy who were observed in an anticoagulation clinic, the cumulative incidence of bleeding was high, but most events were not life-threatening. The graph shows rates of serious, life-threatening, and fatal bleeding (severity defined in text) over 8 years of follow-up (adapted from Fihn et al,[19] with permission).

Older age has traditionally been considered a risk factor for bleeding and a relative contraindication for anticoagulation for that reason. Most clinicians are reluctant to anticoagulate elderly patients, yet this is the age group in whom thromboembolic complications with atrial fibrillation are most likely to develop. The Framingham study found an annual thromboembolic risk of 4.9% in patients aged 70 to 79 years and 7.1% in those aged 80 and older.[7]

The data on age alone as a risk factor for bleeding while on anticoagulation therapy are conflicting. Prospective and retrospective data on warfarin-related bleeding, broken down by age categories after adjustment for other known risk factors, showed that the risk did not increase stepwise with age older than 50, and confidence intervals were overlapping.[19] A recent Dutch study, however, suggested that age alone is a risk factor.[21] Certainly in older patients, the risk of falls and the ability to comply with therapy need to be carefully assessed before long-term warfarin anticoagulation is initiated.

Risk factors that definitely increase the incidence of hemorrhagic complications of warfarin therapy include a higher intensity of anticoagulation, recently initiated treatment (due to dose adjustment and possible overanticoagulation), an underlying anatomic lesion, and a previous episode of bleeding, particularly in the gastrointestinal tract. Those that probably contribute to a bleeding risk include hypertension, a history of stroke, alcohol abuse, and variability (instability) of the PTR, requiring frequent dose adjustments. Conditions reported to increase the incidence of bleeding (but which are not supported by most data) are female sex, smoking, diabetes mellitus, atrial fibrillation, and congestive heart failure.

Aspirin Therapy in Atrial Fibrillation

The randomized trials establish the efficacy of warfarin therapy in reducing the stroke risk of atrial fibrillation. What about aspirin therapy as an alternative? The annual rates of thromboembolic events for each of the trials with a randomized arm of aspirin are shown in Figure 3.[10,11,15] In the AFASAK study, taking 75 mg of aspirin per day did not confer benefit over taking a placebo, with each arm having an annual stroke incidence of 5.5% per year. The SPAF I and II trials both showed a reduction in the incidence of stroke events with a regimen of 325 mg of aspirin a day in patients younger than 75 years, with less benefit in those older than 75. In SPAF II, a regimen of 325 mg of aspirin a day was less efficacious than the use of warfarin, but was associated with less bleeding. In patients older than 75 in the SPAF II trial, the incidence of stroke with notable residual effects (ischemic or hemorrhagic) was 4.3% per year with aspirin therapy and 4.6% per year with warfarin therapy.[15] Despite close monitoring, the SPAF II study showed a clear increase in the

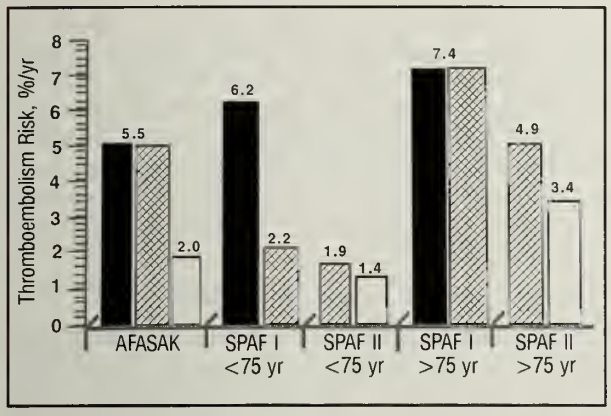

Figure 3.—The annual risk of thromboembolism occurring on aspirin therapy is shown for the control arm (**dark bars**), patients receiving aspirin (**hatched bars**), and those receiving warfarin sodium (**white bars**) for each randomized trial of aspirin therapy in patients with nonvalvular atrial fibrillation. The daily aspirin dose was 325 mg in each study except the Atrial Fibrillation, Aspirin, Anticoagulation study of Copenhagen (AFASAK), in which the dose was 75 mg. Warfarin had greater efficacy than aspirin in all studies, with aspirin of some benefit in the Stroke Prevention in Atrial Fibrillation studies (SPAF) of patients <75 years.

risk of all major hemorrhages in the older age group. As noted earlier, bleeding rates in SPAF II were greater than in the other trials and the intensity of anticoagulation higher than currently recommended. Aspirin taken by patients in the control group of the BAATAF study was not beneficial. Although the benefit from aspirin is debated, the data for the use of warfarin in patients with atrial fibrillation are currently more convincing than those for the use of aspirin.

To summarize, all the randomized trials showed efficacy of warfarin therapy in lowering the stroke risk of nonvalvular atrial fibrillation. Carefully monitored patients have a low risk of major bleeding (2% to 4% per year) on warfarin therapy, although it is possible that more intensive anticoagulation in older patients is associated with a greater bleeding risk. Practice guidelines by the Third American College of Chest Physicians Conference in 1992 strongly recommend long-term warfarin therapy for patients with nonvalvular atrial fibrillation, with the intensity of anticoagulation in the INR range of 2.0 to 3.0.[22] In older patients, the benefits of warfarin need to be balanced with a possibly greater bleeding risk.[23] The use of aspirin in a 325-mg-a-day dose is indicated principally for patients who are poor candidates for warfarin anticoagulation.

Anticoagulation in Valvular Atrial Fibrillation

Valvular heart disease is associated with a greatly increased risk of thromboembolism, and warfarin therapy reduces this risk, although there have been no randomized trials.[24,25] Mitral stenosis is the primary lesion associated with embolism, and the risk increases sevenfold if atrial fibrillation is present. The use of warfarin is strongly recommended in all patients with valvular atrial fibrillation, regardless of whether the fibrillation is chronic or intermittent, in the INR intensity range of 2.0 to 3.0.[26] For those with prosthetic valve replacement, a higher intensity of INR of 2.5 to 3.5 is recommended for mechanical valves. Patients with tissue valves should be anticoagulated with an intensity of 2.0 to 3.0.

Lone Atrial Fibrillation

A subset of patients with atrial fibrillation are known to do well without anticoagulation. The term "lone atrial fibrillation" was coined in 1954 for those without cardiovascular disease or hyperthyroidism.[27] In a Mayo Clinic (Rochester, Minnesota) study of lone atrial fibrillation spanning 30 years, 97% of all cases of atrial fibrillation were excluded.[28] Three fourths of the patients had intermittent atrial fibrillation. Patients were all younger than 60 years (mean age, 44) and carefully selected to exclude any associated medical conditions, such as cardiac or pulmonary disease, treated hypertension, or diabetes. After 15 years, a stroke had developed in only 1.3%, for an annual rate of 0.4%.

The low risk of lone atrial fibrillation was confirmed in two other studies, with mean ages of about 55 years and all patients in chronic atrial fibrillation, having event rates of 0% to 0.2% per year.[9,29] Patients reported to have lone atrial fibrillation in the Framingham study had a 2.6% annual risk of thromboembolic events, but their mean age was 70 years and about a third had hypertension[30]; most would have been excluded by the Mayo Clinic criteria. Lone atrial fibrillation, when carefully defined as atrial fibrillation in patients younger than 60 without systemic or cardiovascular disease, accounts for 5% or less of all cases of atrial fibrillation. The risk of thromboembolic events is less than 0.5% per year, and anticoagulation is not indicated for such cases, whether intermittent or constant, in patients younger than 60. For the uncommon circumstance where an elderly person meets the criteria for lone atrial fibrillation, optimal management is unknown. The annual stroke risk is 2.1% in subjects aged 70 to 79 years diagnosed with lone atrial fibrillation.[31]

Intermittent Atrial Fibrillation

Intermittent atrial fibrillation includes paroxysmal atrial fibrillation of sudden onset lasting a few hours and that persisting for a few days intermittently. The prospective data come from the SPAF I and BAATAF trials, with 34% and 17% of total patients in intermittent atrial fibrillation, respectively (combined 435 patient-years of observation).[12,13] The SPAF study found annual thromboembolic rates of 2.3% in those on warfarin therapy and 7.4% for those on placebo, no different from the rates in patients with chronic atrial fibrillation. The patients with intermittent atrial fibrillation in the BAATAF study had a thromboembolic rate of 1.3% per year, compared with 1.6% in patients with chronic atrial fibrillation, but there were few embolic events overall.

Retrospective studies of intermittent atrial fibrillation have shown a thromboembolic risk of 2% per year during

1,026 patient-years of observation.[32,33] The risk in the largest study was 6.8% in the first month of intermittent atrial fibrillation, but then decreased to 2% annually thereafter, unless chronic atrial fibrillation developed, when the risk increased to 5% per year.[32]

Another retrospective study found a 5% annual risk of thromboembolic events in 431 patient-years observed.[34] Mortality data from an insurance cohort found that the incidence of paroxysmal atrial fibrillation increased twofold in mortality compared with that in sinus rhythm controls, but less than in patients with chronic atrial fibrillation who had a sevenfold higher mortality than controls.[35] Because the risk of intermittent atrial fibrillation appears greater than that for sinus rhythm, these patients should be considered for anticoagulation, particularly those who remain in fibrillation for several days at a time.

Recurrent Stroke in Atrial Fibrillation

Atrial fibrillation is associated with a high risk of recurrent stroke, with the greatest risk being shortly after its onset. Between 15% and 30% of patients will have a recurrent stroke in the first year, and the lifetime risk is 30% to 75%, with the highest risk being for valvular atrial fibrillation.[6,36] A third of recurrent strokes are nonembolic.[37]

In a recent European multicenter trial, 1,007 patients with atrial fibrillation with a history of transient ischemic attack or minor ischemic stroke in the previous three months were randomly assigned to take warfarin sodium, 300 mg of aspirin, or placebo.[38] The annual incidence of stroke was significantly reduced from 12% in the placebo group to 4% in the group taking warfarin. Aspirin had no notable benefit over placebo. The annual rates of the incidence of major bleeding were 2.9% with warfarin therapy, 0.9% with aspirin therapy, and 0.7% with placebo. Nonrandomized studies also suggest that the use of warfarin is beneficial in preventing recurrent stroke in patients with atrial fibrillation who have had a stroke.[6] The recommended anticoagulation intensity for patients with atrial fibrillation and stroke is an INR of 2.0 to 3.0, with higher levels of 2.5 to 3.5 for those in whom a stroke develops while they are on lower intensity anticoagulation.[12]

Management of Newly Recognized Atrial Fibrillation

All patients with newly recognized atrial fibrillation must be evaluated for associated hyperthyroidism. Elderly patients may present with "apathetic hyperthyroidism," with atrial fibrillation as the only apparent clinical feature. Echocardiography is useful to detect valvular heart disease and evidence of silent coronary artery disease, such as infarcts and impaired left ventricular function. Despite extensive data about individual left atrial variables, no single measurement consistently predicts successful cardioversion or the maintenance of sinus rhythm after cardioversion. Left atrial enlargement should not preclude attempts at cardioversion.

The presence of thrombi in the atria or left atrial appendage is helpful in making anticoagulation decisions, but transthoracic two-dimensional echocardiography is poor at detecting atrial thrombi. Transesophageal echocardiography is far more accurate in detecting thrombi, because the esophageal view allows better visualization of the posterior aspects of the valves and atrial chambers. Transesophageal echocardiography is a costly endoscopic procedure, however, requiring close observation, and it is not recommended for the routine evaluation of atrial fibrillation and stroke.

Cardioversion of Atrial Fibrillation

The risk of embolism in cardioversion of atrial fibrillation without anticoagulation is 1% to 5%, and it is reduced to less than 1% with anticoagulation.[22,39-41] Emboli have been reported as long as ten days after cardioversion. Transesophageal echocardiography with the administration of heparin has been proposed before cardioversion to rule out thrombi and to avoid the need for warfarin before cardioversion.[42] The procedure is expensive, however, and safety has not yet been established in controlled trials. Cardioversion itself may precipitate embolic events, regardless of the presence or absence of an atrial thrombus on transesophageal echocardiography before the cardioversion.[43]

Because atrial activity may not return to normal immediately or for several weeks after sinus rhythm is restored, patients would still be at risk after cardioversion without warfarin therapy. Screening with transesophageal echocardiography is not an acceptable substitute for warfarin anticoagulation before cardioversion. Warfarin anticoagulation is recommended before and after cardioversion for stable patients with atrial fibrillation present longer than 48 hours.[44,45]

The use of antiarrhythmic agents improves the likelihood of successfully maintaining sinus rhythm after cardioversion. A meta-analysis of pooled results from randomized, controlled trials of quinidine in patients with atrial fibrillation showed that 69% of patients were in normal sinus rhythm three months after cardioversion, compared with 45% of those taking placebo.[46] By six months, sinus rhythm persisted in 58% and 33% of those treated with quinidine and placebo, respectively. At 12 months, 50% of the group taking quinidine were still in sinus rhythm, compared with only 5% of the placebo group. The mortality odds ratio of quinidine was 2.98, however. Sotalol hydrochloride, a β-blocker with antiarrhythmic properties, and low-dose amiodarone appear to have lower mortality profiles than other agents.[47-49] Concern about increased mortality with antiarrhythmic drugs has led many clinicians to discontinue them short term after cardioversion and to observe the patient for recurrence. In patients who tolerate atrial fibrillation poorly, long-term antiarrhythmic therapy after cardioversion is indicated.

Clinical Strategies

Based on the literature on atrial fibrillation and study results reviewed, clinical strategies can be developed for managing patients (Figures 4 and 5).[44] Absolute contraindications to anticoagulation include an underlying

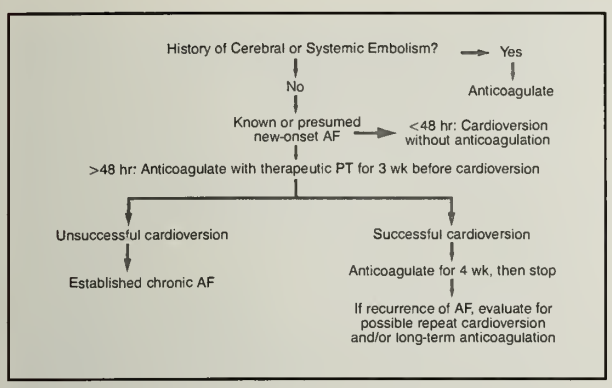

Figure 4.—Therapy for newly recognized atrial fibrillation (AF) requires assessing for previous episodes of embolism and the duration of AF, as shown in the algorithm (modified from Wipf and Lipsky[44]; published with permission of the *Archives of Internal Medicine*). PT = prothrombin time

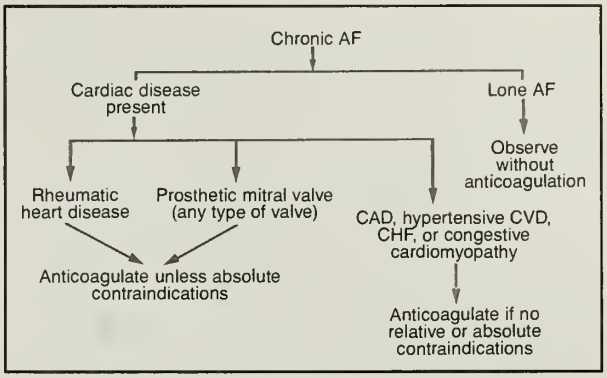

Figure 5.—Therapy for established atrial fibrillation (AF) and recommendations for anticoagulation depend on the associated medical conditions (modified from Wipf and Lipsky[44]; published with permission of the *Archives of Internal Medicine*). CAD = coronary artery disease, CHF = congestive heart failure, CVD = cardiovascular disease

hemorrhagic diathesis; neurosurgical therapy within the past six weeks; recent major trauma; persistently uncontrolled hypertension with diastolic pressures over 105 mm of mercury; a gastrointestinal lesion with recurrent bleeding; and active bleeding from the gastrointestinal, genitourinary, or respiratory tracts. Relative contraindications to anticoagulation include a history of hemorrhage, substantial renal or hepatic disease, active alcoholism, those at risk for falls, a history of noncompliance, or an inability to carefully monitor the patient.

Warfarin therapy is required short term before and after cardioversion unless a patient is hemodynamically unstable or has been in atrial fibrillation less than 48 hours. Patients should be on warfarin therapy with a therapeutic PT INR range of 2.0 to 3.0 a day for three weeks before cardioversion, and warfarin therapy should be continued for a month or two after cardioversion. If cardioversion is unsuccessful or atrial fibrillation recurs soon after, patients should be evaluated for long-term anticoagulation or to repeat the cardioversion.

Warfarin anticoagulation is strongly indicated for patients with atrial fibrillation associated with rheumatic heart disease, prosthetic mitral valves of any type, or a previous embolism (stroke or transient ischemic attack). In the absence of any contraindications, warfarin therapy is indicated for patients with atrial fibrillation with a known cardiac thrombus or with associated nonvalvular cardiac disease, including coronary artery disease, congestive heart failure, cardiomyopathy, and hypertension. Patients older than 75 years with atrial fibrillation may have an increased risk of substantial bleeding on warfarin therapy with a higher intensity of anticoagulation, even when closely monitored, as in the SPAF II trial. Because several other studies have shown benefit and safety of the use of warfarin in the elderly at a lower intensity of anticoagulation (INR 2.0 to 3.0), warfarin use should be considered in this age group, because they are at a particularly high risk of stroke. Aspirin use is indicated for persons with atrial fibrillation who are poor candidates for warfarin therapy because of risk factors for bleeding. Anticoagulation is not recommended for patients younger than 60 with lone atrial fibrillation or for those with pure atrial flutter, which carries a low risk of thromboembolism.

Because the thromboembolic risk of paroxysmal atrial fibrillation in nonvalvular heart disease is greater than for sinus controls, anticoagulation should be considered.

Guidelines for Management of Warfarin Therapy

Warfarin therapy requires close monitoring with frequent laboratory PT measurements and a careful review of complications and medication interactions. To initiate warfarin therapy, low starting doses of 2.5 to 5.0 mg daily are associated with fewer bleeding complications than the common practice of 10 mg daily for three days.[50] The prothrombin time should be checked within three to five days of starting warfarin and then weekly until it has become stable. Monitoring should then be done every four to six weeks and the anticoagulation dose adjusted as needed, with a careful review of medications, diet, and bleeding symptoms. Myriad drug interactions can occur with warfarin, many causing unpredictable fluctuations in PT. The physician ordering anticoagulation must ensure appropriate patient follow-up and may work with an anticoagulation clinic, pharmacist, or nurse practitioner for frequent monitoring. Patients must be educated about their indications for warfarin therapy, the need for careful monitoring, and alterations in physical activity to minimize bleeding risk.

Summary

Several issues remain unresolved in the management of atrial fibrillation. The benefit of a lower intensity of anticoagulation of less than an INR of 2.0 is being studied in an ongoing Dutch trial, PATAF, with patients randomly assigned to different intensities of anticoagulation. The

relative efficacy and safety of warfarin versus aspirin for the primary prevention of stroke in patients older than 75 years of age is controversial. The safety of antiarrhythmic drugs to maintain sinus rhythm has not been directly compared with that of long-term anticoagulation for atrial fibrillation.

Returning to questions asked about the clinical case presented, the cause of atrial fibrillation was nonvalvular heart disease, with a risk of thromboembolism of 5% per year. Whether the patient should have received electrical cardioversion is debatable. He tolerated the arrhythmia well and had prolonged pauses on quinidine therapy. Other antiarrhythmics for cardioversion may have been considered, but with concern about their increased mortality risk, long-term anticoagulation for chronic atrial fibrillation is a reasonable alternative. The development of an embolic event on warfarin therapy appears to be related to inadequate anticoagulation with an INR of 1.4. In the future, this person should benefit from resumed warfarin treatment that aims for an INR in the range of 2.5 to 3.5.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology—Head and Neck Surgery

Terence M. Davidson, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association, and the summaries were prepared under the direction of Terence M. Davidson, MD, and the panel.

Guidelines for Managing Chronic Otitis Media With Effusion

EAR INFECTIONS IN CHILDREN result in substantial economic cost to society. Persistent middle ear effusions that result in conductive hearing loss are implicated in delays or permanent limitations of speech, language, and cognition. Otitis media is the most common illness diagnosed by office-based physicians for children younger than 15 years, and tympanostomy tube placement in children for recurrent acute otitis media or chronic otitis media with effusion is the most commonly performed operation in the United States requiring general anesthesia. Children younger than 3 years are in their greatest period of language acquisition and therefore have the most to lose developmentally from a persistent hearing loss.

Because of the economic and developmental effects of otitis media with effusion in children, the US Department of Health and Human Services has sponsored the development of a clinical guideline for treating otitis media with effusion in children. This guideline applies to children between the ages of 1 and 3 years with no craniofacial, neurologic, or sensory abnormalities. The target child is asymptomatic, without signs or symptoms of acute otitis media, yet has otitis media with effusion. Pneumatic otoscopy is the main diagnostic tool, with tympanometry suggested as a method to confirm the presence of an effusion. After six weeks of an effusion, the administration of oral antibiotics is a therapeutic option. Parenteral decongestants, antihistamines, and oral steroids are not recommended at any time to treat the effusion only. Adenoidectomy or tonsillectomy is not recommended at any time for the management of effusion. Signs and symptoms unrelated to effusion—nasal congestion, allergic disease, nasopharyngitis—are not addressed by this guideline. Environmental risk factors for otitis media should be controlled at all times.

After three months of effusion, the patient's hearing is assessed using techniques appropriate for the age of the patient and the availability of audiologic services. A 20-dB or worse bilateral hearing loss should be treated with antibiotics or bilateral tympanostomy tube placement. Children with an effusion for four to six months and a 20-dB or worse bilateral hearing loss should receive tympanostomy tubes in both ears. An audiologic assessment is appropriate whenever concern arises regarding a child's hearing status.

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Benign Positional Vertigo

A PATIENT'S COMPLAINT of dizziness can be nearly as troubling to the physician as it is to the patient. Most forms of dizziness, however, can be diagnosed in the office based on the results obtained from a precise history and physical examination. Benign positional vertigo is one such disorder that can be readily diagnosed by primary care physicians. Furthermore, new insights into the pathogenesis and treatment of this disorder have allowed for the development of simple, office-based therapeutic maneuvers that are highly effective at eliminating positional vertigo.

The history of a patient with benign positional vertigo is that of true rotatory vertigo elicited by a rapid head movement in a nonaxial plane—such as rolling over in bed or looking up to obtain an item on a shelf. Patients will usually steady themselves, and the vertigo will resolve within seconds (usually <1 minute), although the patient may feel unsteady, nauseated, or frightened for a longer period of time. Although this classic history is diagnostic for this disorder, evidence for the diagnosis may be derived from the physical examination by the performance of the Dix-Hallpike maneuver. In this test, the pa-

tient moves from a sitting to a supine position with the head hanging over the end of a bed and rotated 45 degrees so that one ear is facing the ground. The maneuver is repeated so that both ears are evaluated. When the affected ear is facing the ground, symptoms of vertigo will develop and an eye examination will reveal a rotatory nystagmus that begins about 10 seconds after the patient assumes the offending position. The vertigo and nystagmus will usually abate within 30 seconds, whereupon returning the patient to a sitting position with the head straight will cause a recurrence of the symptoms and a reversal of the direction of the nystagmus, although usually with less intensity.

Benign positional vertigo may affect people of all ages and of either sex. It is most frequently idiopathic in origin, but it may result from head trauma or a viral infection of the inner ear or vestibular nerve (labyrinthitis or vestibular neuronitis). It is thought to result from organic debris depositing itself within the posterior semicircular canal of the inner ear. This debris may originate from the inner ear's otolith organs and may be free-floating within the posterior canal or deposit itself on the cupula of the posterior canal.

The prognosis for patients with positional vertigo is excellent, with the symptoms ultimately resolving in more than 90% of patients. This may take months, however, during which time the patient may have difficulty performing activities of daily living. Some patients may even refrain from physical activities and restrict themselves to bed rest. This further hampers their recovery, as the resolution of symptoms seems to depend on maintaining physical activity.

Within the past decade, two simple treatment modalities have been developed that allow for the rapid resolution of benign positional vertigo and the nearly immediate return of patients to a normal level of function. These maneuvers are designed to rid the posterior canal of the offending debris. The Epley maneuver is more popular in North America because it is better tolerated by patients, and therapeutic results have been better documented. In this maneuver, a patient begins in a sitting position and is then placed supine, with the head hanging over the edge of the bed and rotated at 45 degrees, so that the affected ear is facing the floor. This maneuver should elicit the characteristic vertigo and nystagmus. Once the symptoms resolve, the patient is maintained in a supine position while his or her head is slowly rotated in the opposite direction, so that the unaffected ear is now facing the floor. The patient's head and whole body are then rotated a further 90 degrees, after which the patient resumes the sitting position. This series of positioning maneuvers allows the organic debris to be cleared from the posterior canal and to fall into the vestibule of the inner ear, where it causes no symptoms and will ultimately be cleared. A vibrating device placed behind the ear during the maneuver seems to increase the efficacy of treatment. The patient is advised to avoid a supine position for 48 hours after the maneuver to minimize the possibility of debris migrating back into the canal. Epley reports that one such treatment will lead to symptoms completely resolving in more than 80% of patients, and repeating the maneuver two to three times improves the efficacy to better than 90%.

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Botulinum Toxin for Hyperfunctional Facial Lines

BOTULINUM TOXIN A has been used for the treatment of focal dystonias since 1984. Such conditions as blepharospasm, torticollis, spasmodic dysphonia, limb dystonia, and hemifacial spasm have all been successfully relieved by administering botulinum toxin into the involved muscles. Although these movement disorders have a central neurologic origin, they respond to focal weakening of their end-organ skeletal muscles by the direct intramuscular administration of botulinum toxin. A similar weakening or neuromuscular blockade of nondystonic muscles can be achieved for cosmetic purposes. Administering botulinum toxin into specific muscles of facial expression leads to a relaxation of the muscles' pull on the overlying skin, thereby reducing hyperfunctional lines.

Botulinum toxin binds irreversibly to neuromuscular junctions and inhibits the release of acetylcholine. A flaccid paralysis or weakness is thus produced in the treated muscle. The effect is overcome as new acetylcholine terminals are generated, and muscle strength and activity return three to six months after treatment. There have been no long-term adverse effects reported with the use of botulinum toxin, but repeated exposure to large doses of toxin (>300 IU in a 30-day period) is thought to increase the risk of antibody formation and therapeutic resistance.

Hyperfunctional facial lines such as frown lines, crow's-feet, and deep nasolabial grooves are common cosmetic deformities. These furrows result from the pull of underlying mimetic muscles of the face. Such lines have been treated in the past by surgical excision, administering silicone or collagen, and chemical peels. Each of these treatments has specific disadvantages, and none addresses the underlying facial muscles that create the function lines. Administering botulinum toxin into the corrugator supercilia (glabellar lines); frontalis (forehead lines); lateral orbicularis oculi (crow's-feet); zygomaticus, levator labii superioris alaeque nasi, and orbicularis oris (nasolabial crease); and platysma (neck bands) specifically induces graded weakening of the muscles responsible for the visible skin lines. Electromyographic guidance is frequently used to assure precise administration into the respective muscles. Diffusion or displacement of the administered

toxin can cause unsightly facial asymmetry, ptosis, or oral incompetence. Excessive toxin causes a loss of facial animation, but low-dose, selective administration can enhance the youthful appearance of the skin without losing expressivity. The toxin is effective for about six months, after which it may be readministered. The cost of evaluation, diagnosis, and treatment with botulinum toxin ranges from $500 to $1,500. Compared with surgical procedures and chemical peels, there is no recovery period for administering botulinum toxin, and the desired effects become apparent within three to five days of administration. Experience with repeated use of botulinum toxin in the treatment of dystonias has not shown any long-term complications. The toxin is most beneficial in patients between 30 and 50 years of age, whose facial lines are due more to muscle pull than to age- and sun-induced loss of skin and dermal elasticity.

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Facial Implants in Head and Neck Surgery

FACIAL IMPLANTS were introduced in the 1950s with the oval cheek and central chin implants. The development of technology in the form of new alloplastic materials and computer-aided design has widely expanded the uses of implants in the head and neck region. Today augmentation procedures are used not only to increase skeletal dimension, but to rejuvenate and correct contours. Contemporary standards demand that facial plastic surgeons have a thorough knowledge about the selection of implants.

With the breast implant crisis, the question of the ideal implant material has come to the forefront of facial plastic surgeons. The ideal implant would be elastic, easily moldable, nonallergenic and noncarcinogenic, and resistant to infection. The ideal implant has not yet been developed.

New materials such as expanded polytetrafluoroethylene (polytef; Gore-Tex) have recently been used successfully as implants in the subcutaneous tissue and the facial, head, and neck regions. Gore-Tex has been used in 3.5 million patients over a 21-year period in vascular grafting and has stood the test of time as a reliable and safe material. Recent studies have demonstrated histologically that there is a limited reaction of the body to this material. It has been used in subcutaneous augmentation and recently as a customized implant material because it is easily moldable and can be fitted to each patient's specific needs.

The use of implants in the facial region has expanded tremendously in recent years due to increased understanding of the anatomic areas to be augmented. In the past the mentum was augmented through a central chin implant. The development of the wrapped-chin implant and the mandibular angle implant has expanded the indications for augmenting the mandibular region and has improved the ability to contour not only the anterior mentum but the prejowl sulci and the mandibular angle. Often with aging, the geniomandibular groove or prejowl sulci deepen, contributing to aging characteristics. The wrapped-chin implant allows the contour in this region to be restored and rejuvenated and augments the rhytidectomy procedure.

Malar implantation can be a difficult and challenging procedure. The expanded concept of zonal regions in the malar area has improved the understanding of selecting an appropriate malar implant. Malar shell implants, combined submalar-malar implants, tear-trough implants, and submalar implants all can be tailored to patients' needs. Critical analysis of a patient's face by the surgeon will ensure appropriate implant selection and will provide the rewards that facial contouring procedures of the midface have to offer.

Computer-aided implants have allowed the application of alloplastic materials to specific facial deformities. The development of this technology has allowed surgeons to customize the implant in areas of congenital or traumatic asymmetric deformities or in cases of customizing implants for aesthetic recontouring. Using computed tomography allows a surgeon to analyze the anatomic subtleties and to devise an implant that models and forms an accurate fit to the underlying bony deformity. Although this technology offers specific advantages, this is generally not often required in standard aesthetic facial contouring. As the technology expands, its application will certainly become more commonplace and allow the customizing of each individual implant. The fact that most facial implant procedures in the head and neck are done using a local anesthesia and on an outpatient basis has substantially reduced the cost and lessened the complications.

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Changing Aspects of Epiglottitis

ACUTE EPIGLOTTITIS is classically described as a *Haemophilus influenzae* type b bacterial infection of the epiglottis in children. Recent epidemiologic studies have recorded a decline in the incidence of epiglottitis in children from 3.47 cases per 100,000 in 1980 to 0.63

cases per 100,000 in 1990 ($P < .001$). Between 1980 and 1990, the annual incidence of acute epiglottitis in adults remained nearly constant at 1.8 cases per 100,000. Consequently, the ratio of the pediatric annual incidence to the adult annual incidence of epiglottitis has dropped from 2.6 in 1980 to 0.4 in 1990, and adults are now at greater risk than children.

The decline in the incidence of acute epiglottitis in children began in 1986, a year after the Haemophilus b conjugate vaccines were introduced to combat more invasive *H influenzae* type b-caused diseases such as meningitis and septic arthritis. The American Academy of Pediatrics currently recommends giving a three-dose regimen of Haemophilus b conjugate vaccine to infants beginning at age 2 months.

Acute epiglottitis in children will not be eliminated. Some children will not receive the vaccine, and others will be incompletely immunized. Other organisms than *H influenzae* type b and other types of *H influenzae* may become major causes of epiglottitis.

Epiglottitis occurs most frequently in children aged 2 to 5 years. A child with acute epiglottitis typically has symptoms of fever, sore throat, odynophagia, muffled voice, dyspnea, stridor, and drooling and often sits erect to improve the airway. Blood cultures are positive for *H influenzae* in 50% to 75% of cases.

Management is begun by stabilizing the airway with an endotracheal tube or, if necessary, a tracheotomy. Treatment with antibiotics against β-lactamase–producing *H influenzae* is initiated. Hospitals should have a treatment protocol established for children who may have epiglottitis.

In contrast to children, most adults do not have signs or symptoms of airway obstruction. Often their only symptoms are sore throat and odynophagia. Some adults do not seek medical attention or are diagnosed as having pharyngitis. Clinicians should suspect epiglottitis in patients who have a severe sore throat and odynophagia, especially if they have a muffled voice or drooling. A routine oropharyngeal examination does not exclude epiglottitis because 56% of patients have a normal oropharynx. Indirect laryngoscopy is the most accurate way to diagnose epiglottitis because, unlike in children, the procedure is much less likely to provoke laryngospasm and airway compromise. As with children, both the supraglottis and the epiglottis may be affected.

Although acute epiglottitis is usually caused by *H influenzae* in children, *H influenzae* is seldom the cause in adults. Blood and oropharyngeal cultures in adults have a low bacteriologic yield, but many organisms have been cultured from the adult larynx.

Medical management in adults includes antibiotic therapy for *H influenzae*, *Staphylococcus aureus*, group A β-hemolytic streptococcus, and *Streptococcus pneumoniae*. The use of parenteral corticosteroids remains controversial and awaits a prospective controlled study.

In adults as well as in children, maintaining an adequate airway is the main concern. Each patient must be evaluated according to a practitioner's clinical judgment. If any question of airway compromise exists, the safest course of action is to secure the airway. Respiratory distress, stridor, and sitting upright are the major signs and symptoms associated with the need for adult airway intervention. Adults who do not have signs or symptoms of upper airway obstruction can be treated medically under close observation in a hospital unit that has staff capable of securing an airway if necessary. Intubation or tracheotomy are necessary for patients who have progressive supraglottic edema or stridor.

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Phonosurgery—Outcomes of Varied Techniques

WITHIN RECENT YEARS there has been pressure on the medical profession to verify the usefulness of surgical procedures. Thus, outcomes research has moved to the forefront as one of the most important areas of scientific investigation. Because laryngology and phonosurgery (surgical therapy to alter vocal quality) are relatively new subspecialties, the clinical efficacy of many of these newer procedures is of general interest.

Several studies have shown substantial sustained improvement in quantitative measures of vocal function following type I medialization thyroplasty for patients with unilateral vocal fold paralysis. (In this procedure, using local anesthesia a small Silastic implant is used to medialize the vocal fold through a window cut in the thyroid cartilage.) In addition, the efficacy of the use of botulinum toxin in the treatment of adductor spasmodic dysphonia has been successfully shown. Whereas thyroplasty improves the voice in patients with unilateral vocal fold paralysis and has been shown to be superior to administering polytetrafluoroethylene (polytef; Teflon), patients after thyroplasty still have problems speaking in loud situations and complain of voice fatigue with extended use. This is related to an inability of the thyroplasty to close a large posterior gap and prevent atrophy of the muscle of the vocal fold. In contrast, adducting the arytenoid and reinnervating the nerve can alleviate these deficiencies, but no randomized studies have been published that compare these techniques on unilateral vocal fold paralysis. Furthermore, there have been no published reports comparing the efficacy of these techniques in patients with paretic or bowed vocal folds due to senile aging or neuromuscular disorders.

Most laryngologists agree that thyroplasty improves the voice in patients with vocal fold bowing 60% of the time and that about one in four have dramatic improvement. These results are probably related to the observation that a weak voice and vocal fold bowing are a result of a number of varied causes, including neuromuscular weakness, loss of the lamina propria, and various neuromuscular disorders such as myasthenia gravis, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and the Shy-Drager syndrome.

In contrast to the efficacy of procedures for adductor spasmodic dysphonia, outcomes research with respect to the treatment of nonadductor forms of dystonic dysphonias has rarely been reported. This is primarily because of the general impression by laryngologists that the abductor and mixed varieties of dysphonias have not shown good responses to current therapies. With abductor or mixed dysphonia, the vocal folds open and close normally during inspiration and phonation; in paretic dysphonia, the vocal fold is immobile.

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Endoscopic Forehead Lift

THE FOREHEAD IS the zone of expression. As we mature, the forehead falls, producing a tired or angry look that results from the triad of fallen brows, wrinkles on the forehead and between the eyes, and overhanging infrabrow skin hooding the eyes.

The customary remedy for a fallen forehead has been a coronal forehead lift, with an incision extending from ear to ear across the top of the head. This procedure has the disadvantage of producing paresthesias—resulting from interrupting the course of the supraorbital nerve—causing hair loss in the large incision line and altering the shape of the hairline.

Endoscopic approaches to lift the forehead were developed in 1989. The procedure has been successful whether the surgeon worked in the subgaleal, subperiosteal, or subcutaneous planes.

The success of the ability to elevate a fallen brow, eliminate forehead wrinkles, and relieve infrabrow skin overhang has been equivalent to that of the standard coronal forehead lifts with incisions in front of the hairline, and the stability of the aesthetic corrections appears comparable over a six-year follow-up. The incidence of complications is diminished when compared with that of the standard procedure: the hair-bearing skin is not resected, the incidence of postoperative paresthesias is diminished, the hairline is not altered, and scarring is reduced. Most surgeons have not increased their charges for forehead lifts, despite the expense of added endoscopic instrumentation.

This procedure relies on the principles of releasing the muscles that held the brow downward and advancing the brow and forehead backward. The posterior retraction of the forehead and brow is fixated to periosteum, and excess skin is removed through a triangular removal of skin through the small incision. Subsequently, a technique of backward fixation has been developed using a screw in the skull. This method of fixation has allowed even these small incisions of 4 to 5 cm to be reduced to 1 cm.

At present, an entire forehead lift can be done through three to five 1-cm incisions. The resolution of frown lines, the elevation of the brow, and the removal of skin hooding over the eyes has proved, over our six-year experience with this technique in 450 patients, to be stable and long lasting.

Whereas women seeking cosmetic rejuvenative operations of the forehead and brow have benefited from these smaller incisions, men with partial or complete baldness are able to raise their brow position without a feminization of their features. Men had often been excluded from forehead operations because of the scarring across a bald head and a posterior advancement of the forehead.

The methods of endoscopic surgery learned from these forehead cosmetic operations have been extended and applied to the reconstructive field. Facial fracture reduction is one of the ways that endoscopic facial plastic surgery has advanced.

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Alerts, Notices, and Case Reports

An Unusual Cause of Dysphagia

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MYASTHENIA GRAVIS has an annual incidence of 3 to 4 per million.[1] The diagnosis is often missed because it is rare and because its symptoms characteristically fluctuate. We report a case of myasthenia gravis in a patient who presented with dysphagia. The patient had been seen by several specialists who had performed a multitude of tests without reaching the correct diagnosis. Symptoms of dysphagia differ according to the cause. Both neuromuscular and esophageal causes must be considered in the evaluation of dysphagia.

Report of a Case

The patient, a 37-year-old man, was admitted to University Medical Center of Southern Nevada (Las Vegas) after three months of progressive dysphagia and an 11-kg (25-lb) weight loss. Six years before admission, the patient had suffered from nasal regurgitation of liquids, with tracheal aspiration and coughing, and diplopia when driving late at night. The nasal symptoms and aspiration resolved spontaneously within three weeks, but the diplopia persisted. Three months before admission, he began having difficulty swallowing solids. The dysphagia worsened, extending during the next two months to liquids. The patient again had nasal regurgitation of liquids, along with coughing from tracheal aspiration. His symptoms were noticeably worse in the afternoon and evening. He saw a gastroenterologist, a surgeon, and an internist. A barium swallow, esophagogastroduodenoscopy, computed tomographic scans of the abdomen and chest, esophageal motility studies, and esophageal manometry revealed a right middle lobe infiltrate and mild gastritis. At the time of admission, he was unable to swallow solids or liquids, but did not have odynophagia. In addition to dysphagia and diplopia, the patient complained of easy fatigability of his middle fingers, which he used extensively in his job as a newspaper carrier. His medical history was notable for head trauma seven years earlier, resulting in the loss of all upper teeth. He recovered fully and had no neurologic deficits.

(Tsung K, Seggev JS: An unusual cause of dysphagia. West J Med 1995; 163:159-160)

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On physical examination the patient was thin but in no acute distress. Mild bilateral ptosis was present, but vision and extraocular movements were grossly intact. He had symmetrical weakness of the facial muscles. His gag reflex was weak, and he was unable to swallow. He could extend his tongue only 1 cm beyond his lips. Speech was markedly nasal and slurred. The rest of the physical findings were within normal limits. Blood chemistry values and blood counts were unremarkable except for a serum cholesterol level of 2.8 mmol per liter (110 mg per dl). Following the intravenous administration of 10 mg of edrophonium chloride (Tensilon), the patient could swallow and speak clearly. His ptosis resolved, and he regained full strength in the muscles of his face and tongue. A serum acetylcholine-receptor antibody titer was later found to be elevated at 12.5 ng per ml. Treatment with pyridostigmine bromide, prednisone, and intravenous immune globulin was begun, resulting in rapid but incomplete improvement. A few weeks later the patient underwent a thymectomy. There were no complications, and no thymoma was found. Prednisone therapy was discontinued, and the patient was maintained on a regimen of pyridostigmine after the operation.

Discussion

In retrospect, our patient had a fairly classic case of myasthenia gravis. The symptom constellation of dysphagia, diplopia, and facial muscle weakness, worsening late in the day, is typical of this disorder.[2] Obtaining a history of nighttime diplopia and fluctuating weakness requires specific, direct questions. A high level of suspicion for myasthenia gravis is necessary. Nighttime examination of patients may be useful. Because the symptoms of the disorder usually fluctuate, the results of a daytime examination may be completely normal. Dysphagia is the chief complaint in only 6% of patients with myasthenia gravis,[3] although 28% exhibit bulbar symptoms—dysphagia or dysarthria—at its onset.[2] Ocular symptoms—diplopia and ptosis—are the chief complaint in 53% of patients with myasthenia gravis. Weakness in the face, neck, trunk, and limbs may also occur; in general, muscular weakness has a highly variable pattern in patients with this disorder.[3]

The patient's major symptom was dysphagia, which, as mentioned earlier, is the main symptom in a minority of patients with myasthenia gravis. Therefore, the evaluation before admission to hospital focused on this symptom. The exact nature of dysphagia can vary depending on the disease that causes it. Dysphagia falls into two major categories: oropharyngeal and esophageal.

In oropharyngeal dysphagia, patients have difficulty with the initial phase of swallowing, that is, transferring a bolus from the mouth to the upper esophagus. The differential diagnosis of oropharyngeal dysphagia includes neurologic disorders (cerebrovascular accident, multiple

sclerosis) and motor unit disorders (amyotrophic lateral sclerosis, progressive bulbar palsy, muscular dystrophy, polymyositis or dermatomyositis, and myasthenia gravis). Symptoms of oropharyngeal dysphagia do not differ greatly in these various diseases. Dysphagia occurs with liquids and solids, and multiple attempts may be necessary to swallow successfully. Nasal and oral regurgitation often occur immediately after a swallowing attempt, sometimes with a forceful spraying of the mouth contents. Tracheal aspiration is common, possibly leading to pneumonia. In severe cases, patients may not even be able to swallow their own saliva, and malnutrition and weight loss may result.[4]

In esophageal dysphagia, the swallowing act is initiated normally, but a bolus of food fails to progress into the stomach. Patients typically describe a feeling of food sticking during swallowing. This sensation is generally in the esophagus but may be referred proximally to the neck, even with a distal esophageal lesion.[5] The differential diagnosis of esophageal dysphagia includes obstructions (rings and webs, benign strictures, and cancers) and motility problems (achalasia, scleroderma). Generally, obstructive disorders (unless severe) cause dysphagia for solids only, whereas motility disorders cause dysphagia for both liquids and solids. Heartburn is typical of scleroderma and strictures. Cancers cause a rapid progression of symptoms, and rings and webs usually cause intermittent dysphagia. Oral regurgitation, but not nasal regurgitation, may occur with esophageal dysphagia, generally hours after swallowing.[4]

Careful questioning can help to determine the cause of dysphagia. If the history suggests myasthenia gravis, an edrophonium test should be done. Although no precise figures have been published, sensitivity is estimated to be about 86% in the ocular form of the disease and 95% in generalized myasthenia—not limited to ocular symptoms. Specificity for the edrophonium test is not clear-cut, but a number of diseases are known to produce false-positive results, including amyotrophic lateral sclerosis and the Guillain-Barré syndrome. A serum acetylcholine-receptor antibody titer is the appropriate second-line confirmatory test, because specificity is high. Sensitivities of 64% (ocular) and 89% (generalized) have been reported.[6] These two tests are accurate and inexpensive enough that they should be done in almost every case of suspected myasthenia gravis.[6,7] Electromyographic techniques (conventional or single-fiber) can also be used to confirm the diagnosis. These techniques have a high specificity, and single-fiber electromyography is fairly sensitive but not widely available. Therapy includes both medical and surgical modalities, and established guidelines are available.[8-10]

In summary, myasthenia gravis is an often-overlooked cause of dysphagia. The differential diagnosis of dysphagia includes oropharyngeal and esophageal causes. When the history suggests oropharyngeal dysphagia, neurologic causes, including myasthenia gravis, must be carefully considered. A directed neurologic history and physical examination, possibly including a nighttime examination, is necessary and sufficient to diagnose most cases of this disorder.

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Nontraumatic Splenic Hematoma Related to Cocaine Abuse

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SPLENIC HEMATOMA and rupture are most commonly seen after blunt abdominal trauma. In rare instances splenic hematomas can occur without trauma, usually in patients with splenomegaly or underlying hematologic disorders.[1,2] This is the first report of a case of an otherwise healthy man in whom a splenic hematoma developed shortly after he used cocaine intranasally.

Report of a Case

The patient, a 40-year-old man who habitually used cocaine, presented to a local emergency department with left upper quadrant abdominal pain radiating to his left shoulder. Seven hours previously, he had "snorted" an unknown quantity of cocaine. He was working on his automobile when the pain began and became progressively severe. In the emergency department, his anterior chest wall was sensitive, but his lungs were clear, heart regular, and an abdominal examination revealed good bowel sounds. His abdominal wall was soft, without

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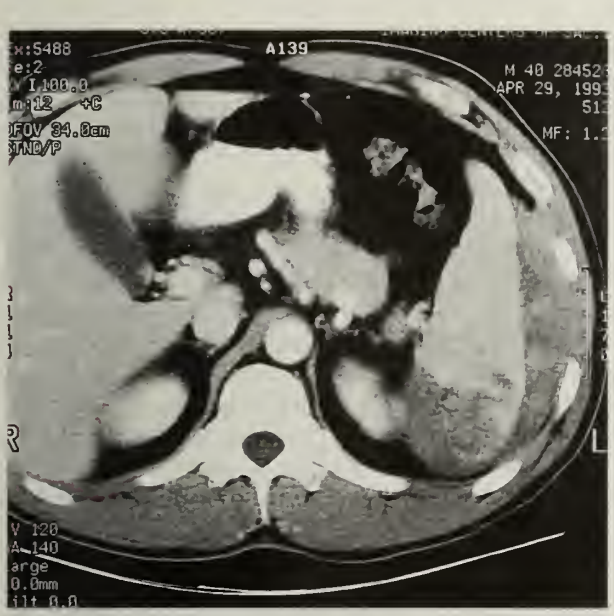

Figure 1.—A computed tomographic scan of the abdomen with contrast shows a subcapsular splenic hematoma and a tear in the splenic parenchyma.

tenderness. Laboratory studies done in the emergency department showed a leukocyte count of 16.9×10^9 per liter (16,900 per mm^3) and a hemoglobin level of 130 grams per liter (13.0 grams per dl). His chest radiograph and electrocardiogram were normal. After determining that a myocardial infarction was unlikely, the emergency department physician sent him home. He was admitted to the hospital a few days later after his private physician diagnosed a splenic hematoma by ultrasonogram.

On examination the patient was afebrile and normotensive. He had tenderness in the left lower abdomen, but his bowel sounds were normal and there was no hepatosplenomegaly, lymphadenopathy, or heart murmur. His left testicle was tender and swollen, but the rest of the examination showed no abnormalities. His leukocyte count was 7.9×10^9 per liter (7,900 per mm^3), a hemoglobin level was 107 grams per liter (10.7 grams per dl), and a platelet count was 172×10^9 per liter (172,000 per mm^3). His prothrombin time was 13 seconds, and a partial thromboplastin time 28.5 seconds. His computed tomographic (CT) scan (Figure 1) showed a splenic hematoma and a possible intrasplenic tear.

The patient's blood count was monitored and remained stable. After a few days of observation, he was discharged home. On follow-up two months later, he had remained drug-free, and his blood count had returned to normal. His testicular swelling and tenderness cleared after treatment with trimethoprim and sulfamethoxazole. A urologist felt that his epididymitis was unrelated to his splenic tear and found no evidence for retroperitoneal dissection of the hematoma. A follow-up CT scan showed almost complete resolution of the splenic hematoma.

Discussion

Cocaine abuse is epidemic and associated with a variety of medical complications.[3,4] This is the first report of atraumatic splenic hemorrhage occurring after cocaine abuse. There was no underlying systemic infection, coagulopathy, or hematologic disorder.

A case has been reported of a woman with the sickle cell trait with infarction of part of her spleen occurring a few hours after she used cocaine intravenously.[5] Conceivably the patient in this report may have first had infarction of a portion of his spleen, then hemorrhage into this area when cocaine-induced vasospasm resolved. Hypodense areas in the spleen could have represented other areas of infarction. The delay in symptoms supports this mechanism because primary hemorrhage (as with intracerebral hemorrhage from cocaine) is usually immediate, but myocardial infarction often occurs hours after ingestion.[6,7] The effects of cocaine on platelet aggregation may be important in both splenic and myocardial infarction.[8-10] The spleen is susceptible to infarction. Other possible mechanisms for his hematoma included arteriolar rupture due to cocaine-induced hypertension or splenic traction while he bent over his car to work on the engine.

Splenic hemorrhage is important to recognize because it can lead to hemorrhagic shock and death. Presenting with left-sided upper abdominal pain radiating to the left shoulder, these patients are often examined for myocardial ischemia. Indeed, this patient was sent home from the emergency department after a cardiac cause for his pain was excluded. With recent reports of cardiac and noncardiac chest pain in cocaine users presenting to emergency departments,[11,12] clinicians may overlook the possibility of splenic injury. If thrombolytic therapy is instituted, an iatrogenic disaster may occur, as this type of therapy in itself is a rare cause of splenic hematoma.[13] Clinicians should therefore include splenic hemorrhage in their differential diagnosis when seeing cocaine-using patients with chest, left upper quadrant, or left shoulder discomfort. Chest pain radiating to the left shoulder is a classic sign of subdiaphragmatic irritation, and a CT scan or ultrasonogram should be strongly considered, even in the absence of pronounced abdominal findings, once cardiac or intrathoracic disease is excluded.

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Hantavirus Infection Following Wilderness Camping in Washington State and Northeastern California

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THE HANTAVIRUS PULMONARY SYNDROME is a newly recognized infectious disease with a high case-fatality rate. Initially described in the Southwest, cases of the disease have now been reported from a wide geographic area in the United States.[1] The clinical consequences of this infection are severe: Of the first 17 cases reported, 50% of the patients presented with hypotension, and rapidly progressive pulmonary edema developed in 15 (88%).[2] As of June 1995, 60 of the 113 patients diagnosed with the hantavirus pulmonary syndrome (53%) have died.[3] The etiologic agent is a previously unrecognized hantavirus, a single-stranded RNA virus that belongs to the Bunyaviridae family.[4-7] Although a uniform nomenclature has not been consistently used to describe this virus, the currently accepted name is *Sin Nombre* virus (Ali S. Kahn, Special Pathogens Branch, Centers for Disease Control and Prevention [CDC], oral communication, July 1, 1995).[1,5,6,8] The primary mode of transmission suggested by epidemiologic studies has been exposure to rodent excreta in and around rural households.[1,9]

(Flood J, Mintz L, Jay M, Taylor F, Drew WL: Hantavirus infection following wilderness camping in Washington State and northeastern California. West J Med 1995; 163:162-164)

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In this report, we describe the case of a patient with the hantavirus pulmonary syndrome who presented to a northern California hospital in the summer of 1992, before the cluster of cases of the syndrome that occurred in the Four Corners region of New Mexico, Arizona, Colorado, and Utah in the spring of 1993. This case is remarkable in that it is the first reported case likely to have been acquired through exposure during wilderness camping in Washington State or northeast California.

Report of a Case

The patient, a 49-year-old woman, was seen in an emergency department in mid-August 1992 with a flu-like syndrome and rapidly progressive dyspnea. She had been in good health until four weeks before admission, when, while she was camping in North Cascades National Park in Washington State, several skin lesions developed on her anterior lower extremities that she attributed to insect bites. She described them as 3 cm in diameter, round, intensely pruritic, raised, erythematous, with a central white area, and resolving within a week.

Two and a half weeks before admission, she had generalized weakness, crampy abdominal pain, nausea, anorexia, and foul-smelling loose stools. These symptoms continued but waxed and waned in intensity. Eight days before admission, she had fever, chills, and myalgias and arthralgias involving the hands, shoulders, elbows, and knees. Subsequently, she had a frontal headache associated with fever to 39.4°C (103°F) and worsening joint pain. Two days before admission, she was short of breath and had a nonproductive cough and persistent fever. The dyspnea progressed until the morning of admission, when she felt she "could not breathe."

About 4½ weeks preceding her illness, she also had camped for three days in the Mono Lake region in the eastern Sierra of California (Figure 1). During both camping excursions, she filtered her water and brought her own food because of "food allergies," storing it separately in her tent. She slept on the ground outdoors or in partially open tents. There were no reported rodent contacts, and no other camper who accompanied her became ill following either trip.

Her medical history was unremarkable; she specifically had no history of immunosuppression, diabetes mellitus, or lung disease. The patient resided in an urban dwelling in Oakland, California, owned a healthy dog, and did not report rodent exposures at her home to her friends or relatives. She worked as a clinical psychologist at a local hospital and was physically active, running as many as 32 km (20 mi) weekly. She did not smoke, drink alcohol, or inject drugs.

On admission, she was in obvious respiratory distress and had a fever of 38°C (100.4°F), a blood pressure of 70/50 mm of mercury, a heart rate of 102 beats per minute, and a respiratory rate of 32 breaths per minute. She was alert, and her head and neck were normal. Her skin had scattered hyperpigmented areas on the lower extremities. Examination of her lungs revealed rales at

ABBREVIATIONS USED IN TEXT
CDC = Centers for Disease Control and Prevention
Ig = immunoglobulin

both lung bases and diminished breath sounds bilaterally. There was diffuse mild abdominal tenderness with voluntary guarding. Her leukocyte count was 11.6×10^9 cells per liter (11,600 cells per mm^2) with 0.50 (50%) polymorphonuclear leukocytes and 0.30 (30%) band forms. The hematocrit was 0.51 (51%), platelet count 91×10^9 per liter (91,000 per mm^2), prothrombin time 14.1 seconds (normal, 10.3 to 13.3), partial thromboplastin time 73.3 seconds (normal, 23.9 to 35.7), and lactate dehydrogenase level 542 U per liter (normal, 80 to 242). Arterial blood gas measurements done while the patient received 100% oxygen by a non-rebreather mask showed a pH of 7.47, Pco_2 of 30 mm of mercury, and Po_2 of 51 mm of mercury with 88% oxygen saturation. A chest roentgenogram showed diffuse interstitial infiltrates with bilateral pleural effusions.

Within the first 24 hours of her hospital course, the patient deteriorated rapidly, progressing to fulminant adult respiratory distress syndrome and shock, requiring mechanical ventilation and vasopressors. Despite treatment with several intravenous antibiotics and aggressive supportive care in the intensive care unit, she died on day 8 of her hospital stay. An autopsy showed pulmonary edema with pleural effusions and interstitial pneumonia. Serum specimens were submitted to the CDC at the time of her hospital admission and revealed no evidence of infection with other pathogens. Following the description of cases of the hantavirus pulmonary syndrome in the Southwest, we asked the CDC to test this patient's serum for hantaviral infection. Serologic tests were positive by immunoglobulin (Ig) G and IgM enzyme-linked immunosorbent assays for hantavirus. Fixed autopsy specimens submitted to the CDC retrospectively also showed lung tissue to be positive for hantavirus by immunohistochemistry.

Discussion

This case demonstrates the typical clinical features of the hantavirus pulmonary syndrome.[2] Specifically, this patient had the early clinical hallmarks of this illness, including fever and myalgia followed by headache and cough, which have occurred in 100% and 71% of the initially described cases, respectively. Abdominal pain has also occurred in 24% and diarrhea in 59% of patients.[2] The ten-day duration of symptoms before admission to a hospital is also consistent with other reports of the syndrome.[2] The notable laboratory findings observed in this patient included leukocytosis with a pronounced leftward shift, thrombocytopenia, a prolonged partial thromboplastin time, and elevated hematocrit and lactate dehydrogenase levels. These last three abnormalities have been associated with increased patient mortality.[2]

Although the clinical course of this patient follows a pattern typical of other published cases, a number of epidemiologic aspects of her illness remain unresolved. Where and how did this patient receive exposure to the hantavirus? From the existing data, she appears to have contracted hantaviral infection while camping in the wilderness. Rodents are the primary reservoir hosts of hantaviruses identified to date, and the deer mouse, *Peromyscus maniculatus*, is the likely reservoir for the hantavirus responsible for the pulmonary syndrome.[9] The virus is shed from saliva, urine, and feces, and humans are thought to acquire infection most often by inhaling rodent excreta.[10] Unlike most other cases of the hantavirus pulmonary syndrome, however, in this patient, there was no evidence of high-density rodent exposure in a residence or building. She did have possible exposure to rodents while sleeping on the ground outdoors. She was possibly at greater risk than her fellow campers because she brought along and separately stored her own food in her tent. This may have resulted in inadvertent contact with rodents or rodent excreta and would explain why the syndrome failed to develop in any other campers on either trip. An additional risk factor may have been the multiple insect bites she acquired in the North Cascades. Whereas arthropod vectors have not been documented to have a role in the transmission of hantaviruses,[11,12] transmission may occur when dried materials contaminated by rodent excreta, such as dirt, are directly introduced into broken skin.[10] This patient's pruritic skin lesions may have provided such a portal of entry.

Although 14 campers accompanied the patient on her trip to North Cascades National Park and 4 camped with her in the Mono Lake area of northeastern California, none of these persons reported similar insect bites and skin lesions. During the Washington trip, only this patient stored her food inside her tent. Food for the

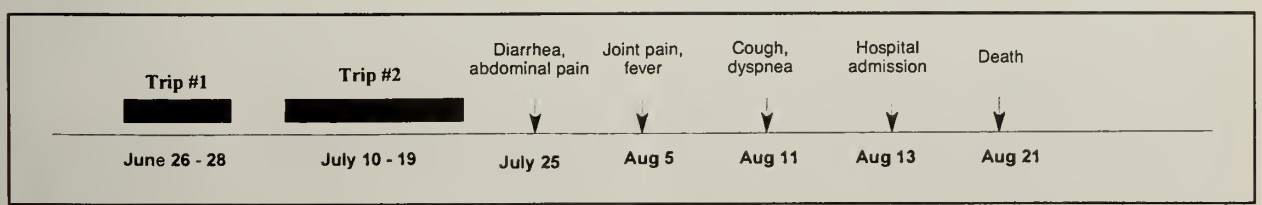

Figure 1.—The onset of the hantavirus pulmonary syndrome following 2 wilderness camping trips is shown. Trip #1 was to Mono Lake, Mono County in northeastern California. Trip #2 was to North Cascades National Park, Whatcom County in northwestern Washington State.

remainder was kept separately at the campsite in a protected storage area. The persons who camped with the index patient have not had serologic tests to determine whether exposure to hantavirus occurred that resulted in subclinical infection.

Although it is probable that she acquired the hantaviral infection while camping, it is less certain whether she became infected in the North Cascades or in the eastern Sierra. The incubation period of this syndrome is not clearly defined. Previous cases suggest an incubation period of three to six weeks. Symptoms developed in this patient 15 days after her first day of camping in Washington State and about four weeks after her visit to the eastern Sierra. She spent 9 days camping in the North Cascades and only 3 days in the Sierra. A survey of campers who accompanied her to these areas revealed no rodent sightings or contact in either location. Although the duration of possible exposure favors Washington State as the source of hantaviral infection, only genotyping of the hantaviral strains in infected rodents in these two areas, with comparison with the patient's hantaviral genotype, would permit a definitive answer.

Unfortunately, the assay for this analysis requires fresh or frozen tissue, which is not available in this retrospectively diagnosed case. Because hantaviral infection of deer mice has been confirmed in most western states including California and Washington, campers should be advised regarding safe food storage techniques and the avoidance of direct contact with rodents and their excreta. Recommendations have been published by the CDC that contain specific precautions for campers and hikers in affected areas.[9]

This report documents a case of the hantavirus pulmonary syndrome occurring nearly a year before the first reported outbreak and extends the possible range of the virus to include northern Washington State. Recognition of the expanding geographic occurrence of the syndrome emphasizes the need for physicians in all of the western states to consider this problem in the differential diagnosis of the adult respiratory distress syndrome. Further investigation of this newly recognized illness will provide clinicians with useful information regarding its incubation period and the risk posed to persons engaged in outdoor activities such as hiking and camping.

Addendum

Since this case was investigated, six other persons with the hantavirus pulmonary syndrome have had probable exposures in the northeastern Sierra Nevada ranges (Michael Ascher, California Department of Health Services, oral communication, July 1995). Given the spatial cluster, Mono County may be the more likely site where exposure to the virus occurred in this patient.

Acknowledgment

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Special Series

We are beginning an experiment in THE WESTERN JOURNAL OF MEDICINE—*a section devoted to incredulity and skepticism. As physicians grow busier, pragmatism and expediency become perhaps irresistible forces. And yet, the key to excellence in the practice of medicine is that physicians should always remain questioning, incredulous, and critical.*

There are a number of areas in medicine in which wisdom has been accepted. Yet, there is value to having this wisdom examined, argued, and dissected. We begin here with a critical analysis by two equally articulate physicians of the issue of screening for cancer. Both authors make valid points, cite appropriate data, but come to somewhat different conclusions. That may be disturbing, but disturbing is better than complacent and may lead to new research and knowledge.

In future sections we hope to address such issues as migraine headaches, parenteral nutrition, the value of technologies, and perhaps new diagnostic and therapeutic processes as they become either faddishly attractive or a standard of practice.

We welcome your comments and suggestions.

FAITH FITZGERALD, MD
University of California, Davis, School of Medicine

Screening for Cancer

Is It Worth It?

FREDERICK J. MEYERS, MD, *Davis, California*

A delay in diagnosing cancer is widely perceived to compromise severely a patient's chance of being cured. The unrealistic expectations of technology and of physicians' capabilities are inconsistent with modern knowledge of the natural history of cancer. Established and recent precepts in clinical oncology and tumor biology emphasize that inherent characteristics of a malignant neoplasm predict its dissemination, rather than a real or perceived delay in diagnosis. The processes of carcinogenesis and dissemination are more nearly simultaneous than sequential. Uncritical belief in the ability of most cancer screening techniques to provide cure through early detection may do more harm than good. Policy and efforts would be better directed to the primary prevention, detection, or reversal of preneoplasia and to improved therapy for established cancer.

(article starts on p 166)

(Meyers FJ: Screening for cancer—Is it worth it? West J Med 1995; 163:166-168)

From the Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis, School of Medicine.

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Useful Despite Its Limitations

STEPHEN J. McPHEE, MD, *San Francisco, California*

Effective primary prevention strategies are currently available for only a limited number of types of malignant neoplasms. In the meantime, the most effective intervention for cancer control is screening for the early detection of cancer in otherwise asymptomatic persons. Screening is probably most useful for cancers wherein the stage at diagnosis is clearly related to curability. Early detection by screening has been shown to lead to a better outcome following the treatment of cancers of the breast, cervix, and colon. Screening for cancer also enables preneoplastic states to be detected and treated. Screening programs offer an opportunity to enhance the potential of chemoprevention. New cancer screening tests will soon be developed, including some that will detect known genetic predispositions to cancer. Each new screening test must be critically evaluated in rigorous studies before being embraced or rejected by clinicians and patients. In particular, screening efficacy must be demonstrated as judged by improved survival of those screened.

(article starts on p 169)

(McPhee SJ: Screening for Cancer—Useful despite its limitations. West J Med 1995; 163:169-172)

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(Meyers FJ: Screening for cancer—Is it worth it? West J Med 1995; 163:166-168)

Patients and physicians fear that the failure to diagnose and treat "cancer" immediately will lead to a greater chance of death or disability. This presumes that there is a disease called cancer that has a predictable course, can be detected early if sought, and if found, can be cured by local treatment of the early primary before it spreads. The common reaction to this model is to call for ever-earlier diagnosis and treatment. Modern concepts of cancer care and biology, however, recognize that most patients who die of cancer do so because of inherent characteristics of the cancer, not a physician's inadequacy or a patient's failure to seek and receive care. The biologic characteristics of metastatic cancer provide information not only to guide policy away from broad-based cancer findings and toward prevention or the reversal of preneoplasia, but also to displace the current conventional wisdom and thereby reduce the prevalence of ill-founded litigation.

Physicians and Patients Against Themselves

The medical profession and the laity, perhaps too much influenced by preliminary research, the results of inconclusive clinical trials, and lay-directed news stories, perpetuate the myth of salvation through the early detection of cancer. This puts physicians at increased legal risk and, perhaps more pernicious, lays the blame for their "advanced" disease on the patients themselves, as they may be told by their physician (and their friends): "If only you had been seen earlier." Moreover, with spiraling upward costs, cancer screening is expensive. Standards of care are established by the profession and by the will of society, particularly in the case of screening for preclinical cancer. New technology raises the customary care to a much higher level and creates an environment of unrealistic patient expectations.[1]

The profession recognizes as necessary the continued debate over and the development of screening programs for cancer. If such investigative programs are proselytized as standard of care before efficacy is shown, and survival is not ultimately enhanced, then the result of such inconsistent information is both individual disillusionment with medicine and societal anxiety. The disillusionment and anxiety produce distrust and litigation.

Three Immutable Factors in Cancer Evaluation

In all patients, a precise prognosis and an appropriate therapeutic program for cancer depend on three factors:

- Histologic analysis of the tumor, including type, grade, and, if possible, the characterization of the genetic features of the cancer cells;
- Stage, the apparent extent of the neoplasm at diagnosis; and
- Comorbid conditions that impair treatment and that predict survival in each patient.

The first two factors are tumor characteristics that predict metastasis. Not only do cancers vary in their metastatic potential, but also one primary type of cancer—such as breast or prostate carcinoma—differs among patients in its potential to disseminate. The third factor determines not only whether the cancer will affect survival, but also a patient's ability to survive rigorous

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intervention if that is called for. This three-point appraisal is especially important in the analysis of nonrandomized studies of screening and treatment interventions for cancer. Such studies have been reported to support a no-treatment approach to selected men with prostatic carcinoma.

Those same studies can also be used to show that a delay in diagnosis is often not clinically relevant. The expected survival of the average white man aged 60, 70, and 80 years is about 19, 12, and 17 years, respectively. In a study of 223 men with untreated prostatic carcinoma observed for an average of ten years, more than half died during the decade, but 91% died of something other than their cancer.[2] Moreover, the rate of tumor growth in these men suggested strongly that earlier detection would have made no difference. So, in indolent tumors with low metastatic potential, particularly in hosts with other diseases or old age, early detection makes little difference. Detection may even cause injury if therapy is more traumatic than the natural course of the disease.

At the other end of the spectrum of the natural history of cancer, certain tumors are so virulent that early diagnosis and therapy have no effect. Adenocarcinoma of unknown primary origin is perhaps the most extreme metastatic cancer. A patient is discovered to have widely disseminated cancer without an identifiable primary lesion. There is no opportunity for cure, particularly with modalities of therapy that emphasize regional treatments, such as surgical intervention or irradiation. These unfortunate patients with advanced cancer need strong reassurances that their actions—or lack of earlier action—were not responsible for their metastases.

Cell Kinetics and the Growth of Cancers

A primary 1- to 2-cm neoplasm represents a distinguishable mass of cancer that is the result of a single cell, of a clonal origin, that becomes 1 billion cancer cells admixed with reactive benign cells. This is equivalent to 30 cell doublings; doubling is not determined merely by cell division, but reflects the net proliferative balance between cell division and cell death. Tumor doubling time is used in standard practice to estimate the pace of advancing cancer and is used to make clinical decisions—for example, whether to resect pulmonary metastases that originate from a sarcoma. The doubling time of most tumors of epithelial origin (adenocarcinoma or squamous cell carcinoma) is measured in months, with a biologic life measured in years.

Two studies of carcinoma of the prostate using sequential serum prostate-specific antigen (PSA) measurement provide in vivo corroboration of growth rates of this tumor.[3,4] In the Baltimore Longitudinal Study of Aging, serum specimens were obtained over decades as part of a serum bank in the study cohort of men.[3] The median doubling time computed from serial PSA measurements during the exponential growth phase was three years (range, 1.5 to 6.6 years) for local cancers and two years (0.9 to 8.5 years) for those that were metastatic. A report of 43 patients with diagnosed but untreated carcinoma of the prostate provides confirmatory evidence, as these patients also had a doubling time measured in years.[4] With relatively slow-growing tumors, therefore, it follows that detecting a primary tumor 6 to 12 months or more before standard diagnosis, as is the case in the screening of asymptomatic persons, would merely be detecting in the midpoint of the cancer's life span. Thus "early detection" of many epithelial cancers is a misnomer, and earlier detection may not improve prognosis, but only assure a longer period during which a patient bears the label and anxiety of having known cancer.

If attaining a critical size were mandatory for the metastatic process to be successful, screening for cancer would be a more uniformly successful enterprise. The metastatic cells that result in a person's death emerge long before a clinical diagnosis, however. Achieving a diagnosis 3 to 12 months earlier by screening than by clinical science is often insufficient to alter the death rate from the cancer being studied.

Cancer Biology Provides Clinical Insight

Tumorigenesis—the growth of a primary—is biologically different from the process of metastasis of that same tumor. The most important implication of this biologic reality as regards screening for cancer is that the size of the primary is a relatively unimportant determinant of the metastatic potential of many tumors.

The phenotype recognized as "a malignant neoplasm" is not a single event, but is the manifestation of an accumulation of many alterations in the genotype. These mutations, either inherited or acquired, include the conversion of proto-oncogenes to oncogenes, the loss of tumor suppressor genes, the loss of metastatic suppressor genes, and the inappropriate production or response to growth factors. In fact, critical mutations—most important, those that permit metastasis—may be phenotypically silent during early tumorigenesis. The accumulation of mutations is not sequential, though they are often pictured as such: a tumor may be either local or benign and abruptly, following one more genetic insult, cascade to immediate metastatic disease. The many genetic alterations required for metastasis to evolve are well reviewed.[5]

Discussion

The concept of screening for earlier detection of a cancer implies a monolithic behavior to a type of malignant lesion. In the most general terms, there are three possible behaviors of cancers.[6] One pattern is that of early and rapid evolution of metastases, a situation in which screening will never improve survival and prevention becomes the only possible early intervention. This is exemplified by the many consensus reports that demonstrate no benefit to the use of screening chest radiographs to detect lung cancer. The death rate from cancer is not reduced, as the metastatic cells successfully implant before the threshold of detection is reached.

In a second group of patients, cancers develop with little metastatic potential and should not be sought for in screening programs. The investigations and the natural history of cancer of the prostate support the hypothesis that delayed diagnosis does not necessarily mean harm. In cancer of the prostate, investigators now advocate not only to delay diagnosis, but also to delay instituting therapy for patients with well-differentiated tumors.[7] This represents an acceptance of the fact that a subset of tumors has a lower or absent potential for metastases and that avoiding treatment-related morbidity is of primary import. Patients with these tumors still should be observed clinically to detect any change in the cancer.

This leaves a third group of patients in whom metastases may emerge in a year or two before clinical diagnosis and in whom early detection by screening may make a prognostic difference. For example, regular mammography in women between the ages of 50 and 64 results in a reduction in mortality of about 33%.[8] So far, only cancer of the breast—and in this highly defined subpopulation of women—has been shown to be changed by early detection by screening. The issue of screening for preneoplastic lesions such as leukoplakia, cervical dysplasia, dysplastic nevi, and colonic polyps is entirely separate.

The implication of the data presented here has already affected current case law as regards medical malpractice. If a delay in diagnosis permits metastases to form in distant sites, then the stage is advanced, the prognosis conclusively altered, and litigation is justified under the law. If earlier diagnosis by screening of an already biologically predetermined metastatic cancer does not improve prognosis, then a physician should not be held liable for the failure to diagnose earlier. Two recent California appellate court rulings have upheld the principle that a plaintiff cannot prevail unless it is probable, not simply possible, that a better result would have been obtained in the absence of the perceived negligence.[9,10] Thus a medical malpractice plaintiff may not prevail unless it is determined that the delay in diagnosis and treatment led to the evolution of metastatic cells and was the probable cause of the plaintiff's injury.

Medical, lay, and legal thought have formally accepted that cancers go through a series of steps that include an initial low stage, to a more advanced local stage, to nodal involvement, and finally, to dissemination. Modern thinking discards such a simple, stepwise progression and, rather, considers carcinogenesis and dissemination as processes much more complex. A convincing argument can be constructed on clinical presentation, cell kinetics, and the natural history of the cancer that an interval of a delay in diagnosis rarely alters outcome. Appreciation of these facts may notably alter the prevalence of malpractice litigation in this area.

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Special Series

Screening for Cancer
Useful Despite Its Limitations

STEPHEN J. McPHEE, MD, *San Francisco, California*

Effective primary prevention strategies are currently available for only a limited number of types of malignant neoplasms. In the meantime, the most effective intervention for cancer control is screening for the early detection of cancer in otherwise asymptomatic persons. Screening is probably most useful for cancers wherein the stage at diagnosis is clearly related to curability. Early detection by screening has been shown to lead to a better outcome following the treatment of cancers of the breast, cervix, and colon. Screening for cancer also enables preneoplastic states to be detected and treated. Screening programs offer an opportunity to enhance the potential of chemoprevention. New cancer screening tests will soon be developed, including some that will detect known genetic predispositions to cancer. Each new screening test must be critically evaluated in rigorous studies before being embraced or rejected by clinicians and patients. In particular, screening efficacy must be demonstrated as judged by improved survival of those screened.

(McPhee SJ: Screening for cancer—Useful despite its limitations. West J Med 1995; 163:169-172)

Cancer is the second leading cause of death in the United States, accounting for almost 24% of all deaths in 1991. Each year in the United States, more than 1.25 million new cases of cancer are diagnosed and more than 540,000 people die of cancer. In addition, some 800,000 new cases of nonmelanomatous skin cancer and 120,000 cases of carcinoma in situ are diagnosed each year.[1,2]

Most cancers are thought to be due to a combination of genetic factors interacting with lifestyle factors and environmental exposures. Recent research has helped to define the molecular basis of malignant transformation and the proliferation of cells. This research suggests that mutations in DNA sequences lead to either an amplification or an increased suppression of oncogenes or to the deletion of tumor suppressor genes (or both). Oncogenes encode for cellular growth factor receptors, growth factors, or other elements of the proliferative mechanisms. Tumor suppressor genes encode for regulatory proteins that normally suppress cellular proliferation. A genetic susceptibility to cancer results from mutations that alter normal cellular regulatory processes. Such mutations may be due to exposure to environmental influences such as ionizing radiation or ultraviolet light, to infectious agents such as the human papillomavirus or the Epstein-Barr virus, or to other unknown factors.

As with most other diseases, preventing cancer has the potential to save more lives than does treating it. The primary prevention of cancer includes measures to reduce or remove risk factors (counseling about stopping or not starting cigarette smoking to prevent lung cancer) or chemoprevention to interfere with the multistage carcinogenic process (administering isotretinoin to prevent oral cancer). Secondary prevention entails screening techniques designed to promote the early detection of disease or precursor states (routine Papanicolaou screening to detect invasive cervical cancer or cervical intraepithelial neoplasia). Tertiary prevention measures aim to limit the effects of established disease (partial mastectomy and radiation therapy to remove and control localized breast cancer).

Primary prevention strategies are the most effective and economical of all methods of cancer control. Effective strategies include risk-factor modification such as stopping, moderating, or avoiding tobacco use, alcohol consumption, and exposure to ultraviolet light or industrial carcinogens; measures to prevent viral transmission such as the use of condoms and barrier contraception methods; dietary changes to decrease fat intake and increase fiber intake; and various chemoprevention regimens. Chemopreventive agents under investigation include vitamins and vitamin derivatives such as

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isotretinoin, prostaglandin inhibitors such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone-suppressing agents such as tamoxifen citrate and finasteride.[2,3]

In the long run, primary prevention strategies have a greater effect than secondary prevention (screening). The National Cancer Institute estimates that even a 30% reduction in tobacco consumption would yield a 10% reduction in the number of cancer deaths, whereas widespread screening for breast and cervical cancer would yield only a 3% reduction. Unfortunately, given our limited knowledge about the causes of cancer, effective primary prevention strategies are currently available for only a limited number of types of malignant diseases.

In the meantime, the most effective intervention for cancer control is screening for the early detection of cancer in otherwise asymptomatic persons. Such detection may be achieved through simple observation (skin or oral examinations), palpation (breast or testicular examinations), or laboratory tests and procedures (Pap smear, sigmoidoscopy, or mammography).

Cancer screening tests ideally should be measured against several criteria before widespread adoption. First, the population to be screened must have a sufficiently high prevalence of the cancer, and affected persons must be likely to comply with subsequent tests and treatments. Second, the cancer must have sufficient morbidity and mortality, effective and acceptable treatment must be available for it, a presymptomatic period must exist during which it is detectable, and its early detection and treatment must yield better results than otherwise. Finally, the test must be able to detect early cancer with sufficient sensitivity and specificity, at low cost and risk, and there must be confirmatory tests that are both practicable and available.

Screening is not useful if no method of early detection exists (cancer of the pancreas) or if there is no apparent localized stage (leukemia). Screening is not useful if it cannot be shown that early detection has an effect on mortality rates. Several randomized, controlled trials of chest radiograph and sputum cytologic screening for lung cancer failed to show a beneficial effect on mortality rates for this common cancer. Screening for ovarian cancer with pelvic examinations, serum markers (CA 125), and transvaginal ultrasonography has not been shown to decrease its mortality rate. For the same reason, there is currently controversy about the usefulness of screening for prostate cancer by digital rectal examination, serum prostate-specific antigen levels, or transrectal ultrasonography.[4]

Early detection by screening has led to an improvement in outcome following the treatment of cancers of the breast, cervix, and colon. For each, efficacy studies have reported findings from asymptomatic persons in the general population.

For breast cancer, convincing evidence exists that regular clinical breast examinations and mammography for women 50 to 69 years of age are effective in reducing mortality from this disease. In the mid-1970s, for example, the Swedish National Board of Health sponsored a trial in which 134,867 women aged 40 and older were randomly assigned to receive either one-view mammography at age-dependent intervals (24 to 33 months) or routine care. At five-year follow-up, the overall breast cancer mortality was 31% lower in the group offered screening, and the estimated relative risk for death from breast cancer among women aged 50 to 74 was 0.61 (95% confidence interval [CI], 0.44 to 0.84).[5] Many other well-conducted controlled trials and case-control studies have varied the number of mammographic views taken, the frequency of mammography, and the duration of screening. All but one of the randomized trials and most of the case-control series have shown clinically—and in most cases statistically—significant reductions in breast cancer mortality among women screened.[6,7] Recently a 5% decrease in breast cancer mortality has been shown among white women in the United States, but not among black women (who generally have lower mammography screening rates). Controversy still exists regarding the use of screening mammography in women aged 40 to 49 and in those older than 70.

Although randomized, controlled trials are not available, many studies have shown that regular screening by Pap tests can decrease the cervical cancer mortality rate in women who are sexually active or aged 18 years or older. In Iceland, for example, the establishment of a comprehensive, centralized cervical cytologic screening program led to a notable increase in the number of cases of severe dysplasia and carcinoma in situ treated, a twofold reduction in the mortality of invasive cervical cancer, and a notable decrease in the incidence of advanced-stage tumors.[8] In the United States, the death rate from cervical cancer decreased by more than 70% between 1950 and 1985 with increasing use of the Pap test. Many studies have found a relationship between Pap test screening intensity and changes in cervical cancer mortality rates over time, and a host of cohort and case-control studies have confirmed its usefulness.[6,7] Although most physicians and patients accept its value, controversy still exists regarding the optimal frequency of Pap smear screening in various segments of the population.

Regular screening sigmoidoscopy in persons older than 50 years appears to reduce the mortality from colon cancer. A careful case-control study of rigid sigmoidoscopy found a 59% reduction in colorectal cancer mortality; the risk of colon cancer death was reduced as much as ten years after a single examination.[9] Here again, controversy continues regarding the age at which to begin and the interval between screening sigmoidoscopies.

For most cancers, standardized staging to estimate the apparent extent of disease at the time of diagnosis is extremely valuable, both for planning treatment and for determining prognosis. In the United States, the American Joint Committee on Cancer's TNM staging system is the most widely used system. It is based on a model that postulates that the untreated primary tumor (T) will gradually increase in size, leading to local invasion, then a spread to regional lymph nodes (N) and, eventually, to distant

metastases (M).[2] Unfortunately, the TNM and other staging systems do not always accurately predict prognosis. For many cancers, the primary tumor is not clinically evident until local invasion or involvement of regional lymph nodes has already occurred. For others, the clinical stage at the time of diagnosis does not take into account variations in tumor biology or aggressiveness. For certain of these tumors, specific pathologic characteristics can be helpful in more accurately defining the prognosis (estrogen and progesterone receptors or proliferative index for breast cancer; histologic grade for sarcoma).

Screening is probably most useful for cancers whose stage at diagnosis is clearly related to curability, that is, for cancers with the highest cure rates reported when the tumor is small and there is no evidence of metastasis. For instance, with breast cancer, the expected five-year survival rate is 85% for patients who are in stage I and 60% to 70% for those in stage II, but only 30% to 55% in stage III and 5% to 10% in stage IV. With colon cancer, the five-year survival rates are 80% to 100% for stage I, 50% to 75% for stage II, 30% to 50% for stage III, and 5% for stage IV disease. With cervical cancer, the five-year survival rate is virtually 100% for carcinoma in situ (cervical intraepithelial neoplasia type III), but decreases to 88%, 51%, and 14% for detection at localized, regional, and distant invasive stages, respectively.[7]

For other cancers, such as small-cell carcinoma of the lung, distant metastases have already occurred, often before the small primary tumor can be detected. Obviously, screening for such cancers is not useful. Screening for other cancers in normal asymptomatic persons, even in "high-risk" segments of the population, is not currently recommended, usually because available screening tests do not meet all of the criteria mentioned earlier.

New cancer screening tests will soon be developed. Each new screening test must be critically evaluated in rigorous studies before being embraced or rejected by clinicians and patients. In particular, screening efficacy must be demonstrated as judged by enhanced survival of screened persons. Studies must also be carefully designed to avoid length- and lead-time biases.

Screening for cancer offers clinicians and patients at least three other benefits. First, such screening enables the detection and treatment of preneoplastic states. In fact, screening examinations usually discover many more precursor states than established cancers. In the United States, cervical Pap smear screening currently leads to the discovery of cervical intraepithelial neoplasia—dysplasia and carcinoma in situ—much more often than invasive cancer. (In 1995, it is estimated that 65,000 new cases of carcinoma in situ of the uterine cervix will occur versus 15,800 new cases of invasive cervical carcinoma.[1]) Sigmoidoscopic screening of asymptomatic persons enables the detection of many more persons with adenomatous polyps—approximately 50 to 100 per 1,000 examinations—than cancers: about 1 to 4 per 1,000 examinations. (Autopsy studies have shown that as many as 10% to 33% of older adults have colonic polyps at death, but only 2% to 3% have colorectal cancer.[7]) The detection of cervical dysplasia enables cervical conization or, in experienced hands, cryotherapy or laser ablation and presumably prevents a progression to carcinoma in situ and invasive cancer. For those discovered to have adenomatous colonic polyps, colonoscopic polypectomy can be undertaken; such therapy appears to reduce the risk of subsequent colon cancer by 90%.[10] In addition, chemoprevention with aspirin and other NSAIDs may be undertaken.[2,3] Using this rationale, screening for preneoplastic lesions of the oral cavity (for leukoplakia) and skin (for dysplastic nevi) has been recommended by some authorities, at least for high-risk persons—those who smoke or who have a family history of melanoma. Further studies are needed of the effect of such screening strategies on the mortality of these cancers.

Second, chemoprevention of cancer is a new and exciting area of cancer control. Screening programs offer an opportunity to enhance its potential. Chemoprevention strategies can be applied to four groups: patients who have previously had cancer (to prevent second cancers); those with preneoplastic lesions; those who are at high risk for neoplasia, whether because of family history, lifestyle, or occupation; and other asymptomatic persons in the general population.[2] Logically, chemoprevention will prove most useful to patients in the second and third groups. Screening can enable a clinician to differentiate patients who are members of these groups and thus to prescribe chemopreventive agents most appropriately.

Finally, new screening approaches will soon be developed to detect known genetic predispositions to cancer. Hereditary predispositions to certain forms of cancer have now been linked to specific molecular events within specific genes. Consider colon cancer, for example. Researchers have recently identified the abnormal gene (adenomatous polyposis coli; *APC*) on chromosome 5 that is responsible for the syndrome of familial adenomatous polyposis. The *APC* gene has been cloned, and the protein it encodes has been characterized. Germline mutations in the *APC* gene resulting in reduced expression or truncated proteins have been identified in more than 90% of families with familial adenomatous polyposis. Researchers have also demonstrated mutations in the *APC* gene in patients with sporadic (nonfamilial) adenomatous polyps and in patients with colon cancer. In addition, the genetic abnormalities in the hereditary nonpolyposis colon cancer syndrome have been located using linkage analysis of large kindreds to specific regions of chromosomes 2, 3, and 7. In recent months, four genes at these sites have been identified and cloned: *hMSH2* and *hPMS1* on chromosome 2, *hMLH1* on chromosome 3, and *hPMS2* on chromosome 7.[11] More than 90% of patients with the hereditary syndrome of nonpolyposis colon cancer have mutations in one of these genes, which appear to have a central role in identifying and repairing sites of DNA base-pair mismatch that may occur during normal DNA replication. Malfunctioning of these "genetic proofreaders" presumably means that errors can accumulate during repeated cell divisions, eventually resulting in malignant transformation.

An important consequence of these discoveries is that it is now possible to use linked genetic markers to identify affected family members of cancer patients and to offer them appropriate preventive measures. For example, polymerase chain reaction techniques can be used to analyze DNA from desquamated colonic epithelial cells in stool for mutant alleles predisposing to colon cancer.[12] Although a number of important questions must be addressed before recommending widespread DNA testing for presymptomatic identification of cancer risk,[13] such techniques may enable more targeted cancer screening of high-risk persons. Such targeted screening may lead to earlier chemoprevention, the detection of lesions, and surgical or other therapeutic intervention, enhancing the possible reduction of cancer mortality rates.

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Commentary

On Losing Face

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Most of us possess the illusion that our inner self shines through, no matter our actual appearance. This "inner beauty" concept helps us face the world each day with some degree of confidence. But when the day comes when a face has to be torn—carved apart because of neoplasia—losing face becomes a type of nightmare from which there is no escape into sudden wakefulness.

It all started so inanely. My wife, who doubles as my barber, noticed a small black speck below my left eye while performing her monthly ritual. I could not see it myself, so it became "out of sight, out of mind." However, as the barbering went on, so did the assertions, in increasingly ominous tones, that I should do something about it.

With a suddenly free period in my day, I made a dash for a friendly dermatologist's office (remembering to, first of all, obtain a "referral" from my "primary care provider"). The dermatologist looked for the spot that so bothered my spouse and finally located and extricated it. We both agreed that even though it was "nothing," it would go to pathology for a pro forma examination—just to be on the safe side.

Two days later, the news came in a phone call. "Melanoma," he told me, but with a "good outcome" if I would attend to it. It struck me as interesting that we no longer refer to this disease as malignant melanoma, even though malignant is just what this critter is. In any case, with an adrenaline surge unusual so early in the morning, I made a discrete call to my primary care physician, asking if he would be kind enough to create a referral through the "third-party intermediary" so that I could see the plastic surgeon of my choice.

I realized that to remove the cancer, I was going to be literally losing face.

On my initial visit, the plastic surgeon plotted out on my face the possible extent of her surgical attack and described how this would be accomplished. I was a little shaken when she decreed that I would probably need three visits to the operating department. It seems that melanoma does not lend itself to frozen sections, and several pathologists and my surgeon would need time to review the specimen derived from each session in the operating room. Given my choice of the surgical procedure done in a comatose state or awake, I chose the latter with a standby anesthetist capable of mainlining in potions needed to keep me still.

The initial procedure went well. I felt no pain, was wide awake at the end, and learned that I had not said anything too scatologic. At home a few hours later, I finally screwed up enough courage to look under the dressing and saw that there was, indeed, less of me. Hastily I applied the local antibiotic, applied a new dressing, and sat through the rest of the day with an icebag pressed against the wound to reduce bleeding.

The morning of the next operation three days later, I was chagrined to learn that the margin of the specimen still showed traces of the enemy, with the result that I would have to continue to be a human salami and have more of my face excised. Under the dreamy anesthetic, I could hear my surgeon and the pathologist discussing how far in each direction the excision should proceed. When I heard "nine o'clock" at one point, I started to recall those World War II movies where the enemy aircraft were at *Twelve O'Clock High*.

Knowing that the future of my face hung on the microscopic vision and wisdom of my pathologist (and surgeon), I passed a restless night of vivid dreams of phantomlike figures, with masks over their faces, running through the streets.

I went to the office, saw patients (apologizing, during each visit, for having the left side of my face in bandages), and worried that the margins were not pristine and that the salami attacks would continue. Fortunately, the pathologist was able to report that my skin specimen was finally clean, and I could move on to the reparative stage of plastic surgery.

The third and final operation, now a week after the process had begun, took place again under local anesthesia with standby anesthesia. Because a considerable portion of my face had ended up in the pathology department, it took more than five hours to remove the remaining portion of my visage from its underpinning and make a flap large enough to cover the large defect; that explained the large swelling, hematomas, and loss of sensation in the left side of my face.

Although I had been warned that I would not be able to work for at least three weeks after the surgical proce-

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dure, I decided I could not survive at home watching television dramas and game shows, so I returned to work. Wearing dark glasses, I appeared to my patients more as a victim of a street brawl than the patient of a plastic surgeon. My pediatric patients were totally unimpressed with my appearance, although their parents did express their concern and sympathy. I felt comfortable enough to join my colleagues for lunch in the hospital cafeteria, which came as a shock to my surgeon when she joined us. I reassured her that she should henceforth look on me as a walking advertisement for her surgical prowess—I was, in effect, her poster boy. It is remarkable how rapidly melanoma became the topic of conversation at that lunch among a wide variety of specialists and family physicians. We agreed that a program in our continuing medical education series should be devoted to that subject.

In retrospect, I cannot look on my surgical procedure as a particularly happy experience. On the other hand, in losing face, I acquired perhaps a little humility and might henceforth empathize better with my patients when they proceed to heart surgery. But I did learn from the reactions of my family, colleagues, and patients that I am generally perceived as a reasonably decent human being—probably the most satisfactory outcome of losing face.

Commentary

Anatomy Lessons

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Standing above the cadaver, I wield my scalpel with my usual trepidation. For the umpteenth time since starting Gross Anatomy, I am momentarily immobilized by the task of dissection and by a sense of being hopelessly unequal to it. I let my gaze fall on the ravaged chest cavity and on the neck that has been excoriated to reveal the various features described in our laboratory manual ("To expose the anterior triangle, reflect the skin posteriorly from the anterior median line . . ."). I am thinking once again that the stray cuts of an inexperienced navigator, the severed vessels and obliterated structures, do not do justice to the memory of the person whose body now lies before my well-meaning but unpracticed hands.

The outsider might suspect, as I once did, that students must dissect a cadaver to gain a familiarity with human anatomic relations that will later be applied to a living body. But this, I have come to understand, is not the foremost purpose of dissection and does not explain why this grueling exercise traditionally is undertaken at the very beginning of medical training. There is a calculated logic in exposing us medical students to anatomy while we are still neophytes, standing uneasily with one foot in the lay world, the other poised to enter the beckoning realm of medicine. In my experience, the lessons derived from anatomy are more philosophical than anatomic, more metaphysical than physical. They force us each to confront our fears of mortality and death and shape our sense of ourselves and our relationship to others in our future incarnation as physicians.

The first lesson—and for me, somehow the most incapacitating—is hubris. Throughout these months, I have wrestled with the notion that, just as a physician possesses the privilege, indeed the responsibility, to probe and manipulate a patient's body, I have the right to practice these things on a cadaver. That is the struggle that engages me when I stand paralyzed before the cadaver or bury myself in the laboratory manual to avoid dissection. It is a struggle that is replayed each time an incision is made, each time the dignity of the human form must be violated anew. Gripping the scalpel, I steel myself with the conviction that my future role justifies the ignoble dispensation of this human body.

In my medical training, I am learning that I must continually redefine the boundaries of my relationship to others. I must do this as I accept the right to dissect cadavers and, later, to ask sensitive and personal questions and to do my first awkward examinations and procedures. As a physician, I will be privileged to share with my patients an extraordinary degree of intimacy and will routinely practice violations of privacy that would not be tolerated in any other profession. It is in this sense that dissection serves as an exercise in presumptuousness, without which we students cannot accomplish the metamorphosis to medical practitioners.

The second lesson, thankfully balancing the first, is humility. I well recall the amazement with which I first considered the exquisite, fanlike array of muscles and tendons in the forearm of a cadaver. For weeks afterward I stared at my own hands, flexing and extending the digits to study the ribbonlike insertions of flexor and extensor digitorum, palmaris, and extensor carpi, and to admire the way the wiry tendons, taut as violin strings, bulged slightly under the skin.

The same hand that has been a source of fascination has proved a formidable challenge in dissection. It is impossible to hold someone's hand with mere surgical intent; even the stiff grip of the cold fingers has an undeniable emotional effect. Holding the cadaver's hand, I reflect that this palm I now dismantle must have clutched a pen, caressed a lover, closed over a child's hand a thousand times. There is still the remnant of pink nail polish on the rounded fingernails; for what special occasion was it meant? Or perhaps for no occasion; perhaps she simply liked to take care of her appearance and went in as usual for her manicure, not knowing that she would die that week.

Humbling, also, is the realization of just how much distortion and disease the human body can withstand. At the next dissection table is the body of a woman with a stomach full of cancer; the white nodules have studded her abdominal cavity like a fungus. Yet she went on for years, brushing her teeth in the morning, laughing and talking, gardening or reading or whatever she did, improbably living despite the cancer invading every organ and recess of her body.

As I enter this room of death each morning, I am becoming cognizant of a final lesson. Here in the anatomy laboratory, we students are confronted daily with the

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fact of our own mortality. We peer continually into the literal face of death. We touch it. Its acrid smell clings to our hands and clothes despite lab coats and vigilant scrubbing. And in the face of death, our discomfort takes expression in various ways—strange dreams, tasteless humor, unexplained outbursts of tears or anger.

A fear of death—our own and our loved ones'—is indeed universal. Often equated with a fear of the unknown, it seems to me rather a fear of the unknowable. Death is that which escapes our most strenuous attempts to control the circumstances of our lives. It is the ultimate refutation of the human search for explication, understanding, and cohesion.

It may be that medicine as a career attracts those of us who harbor a particularly strong fear of death, inasmuch as we are prepared to devote our lives to combatting it. As students, we may defend against this fear by distancing ourselves from death: by objectifying cadavers, isolating body parts, covering the face and hands. This foreshadows the way in which we as physicians might protect ourselves by creating psychological barriers between ourselves, the invincible healers, and our vulnerable patients. We physicians create this boundary, as insubstantial as a line drawn in the sand, and we expect death to respect it.

In the anatomy laboratory, my classmates and I have the first of many chances to confront the fear of our own mortality. If we can accept death's inevitability, for ourselves as well as our patients, we can better appreciate each moment of our lives rather than waiting for those lives to begin—after medical school, residency, marriage, a family. And, perhaps most crucial to our development as physicians, the experience will help us bring empathy and compassion, rather than distance and denial, to our interactions with patients.

Editorial

Warfarin Sodium or Aspirin Therapy to Prevent Stroke in Nonrheumatic Atrial Fibrillation

Answered and Unanswered Questions*

THE ROLE OF WARFARIN sodium anticoagulation in preventing strokes in patients with atrial fibrillation is reviewed by Wipf elsewhere in this issue.[1] Although anticoagulation is a highly effective therapy, and we may get the impression that everyone with atrial fibrillation should be anticoagulated, many (maybe even most) patients with nonrheumatic atrial fibrillation should probably not be treated with warfarin. Why? The answers will be addressed by the following questions.

• *Who gets atrial fibrillation?*

One of the most striking features of atrial fibrillation is that it is a disease of aging. The prevalence in patients younger than 50 years is less than 1%, whereas the prevalence in those older than 80 is 10%.[2] The average age of onset of atrial fibrillation is 70 to 74 years,[3] and the median age of people with atrial fibrillation is 75.[2]

• *What is the stroke risk in nonvalvular atrial fibrillation?*

The stroke risk on average in untreated patients with nonvalvular atrial fibrillation is about 5% per year for overt stroke. Perhaps another 1% to 2% per year have peripheral embolization, transient ischemic attacks, or "silent" strokes detectable only by imaging.[4]

• *Does warfarin therapy reduce the stroke risk when used for primary prevention?*

Definitely. Five randomized trials of primary stroke prevention provided concordant results showing an average 68% reduction in the risk of stroke with warfarin therapy compared with no warfarin therapy.[5]

• *Does taking aspirin reduce the stroke risk when used for primary prevention?*

Probably. The estimated pooled reduction of stroke risk with aspirin therapy compared with that in controls is 36% in primary prevention studies.[5] The available trials had conflicting results. The Copenhagen AFASAK trial used a regimen of 75 mg a day and showed an 18% reduction in the incidence of stroke (not significant),[6] whereas the SPAF I [Stroke Prevention in Atrial Fibrillation] trial used a regimen of 325 mg a day and found a significant 44% reduction in the incidence of ischemic stroke or systemic emboli.[7]

• *Which is better for primary prevention, aspirin or warfarin?*

From the available trials, the risk reduction with warfarin therapy (about 68%) has been greater than with the use of aspirin overall (about 36%).[5] In one of the primary prevention trials, the use of aspirin was substantially less effective than warfarin therapy.[8] The largest trial that directly compared the use of aspirin and warfarin, SPAF II, randomly assigned 1,100 patients and found no significant benefit of warfarin therapy (international normalized ratio [INR] 2.0 to 4.5; mean, 2.6) over aspirin, 325 mg a day, in patients either older or younger than 75. Although there were nonsignificant trends suggesting a lower primary event rate in the younger cohort treated with warfarin (0.7% versus 1.3% per year), there were no statistically significant differences between aspirin and warfarin therapy in any of the end points.

• *In secondary prevention, which is more effective, aspirin or warfarin?*

A previous stroke or transient ischemic attack (TIA) has been identified as an important independent risk factor for subsequent events in multivariate analyses.[5,9,10] The European Atrial Fibrillation Trial (EAFT) specifically evaluated therapy in these high-risk patients with atrial fibrillation and previous stroke or TIA,[11] comparing the use of aspirin, 300 mg per day, with warfarin and with placebo. The use of aspirin for secondary prevention in the EAFT trial reduced the risk of recurrent stroke by an insignificant 14% (aspirin: 10% per year; placebo: 12% per year),[11] whereas warfarin therapy was clearly superior to the use of aspirin, reducing the stroke risk by 66% (warfarin: 4% per year; placebo: 12% per year). Another randomized trial in secondary prevention comparing therapy with the platelet inhibitor indobufen with warfarin therapy will be reported soon.[12] On the basis of the EAFT trial, warfarin is definitely the therapy of choice for patients with previous TIA or stroke.

• *Are these results generalizable to "real" patients?*

One problem with the available trials is that a rather special group of patients was entered. Two of the trials reported the percentage of all screened patients with atrial fibrillation who were entered, which was only 6% of patients in the Canadian Atrial Fibrillation Anticoagulation (CAFA) trial[13] and 8% in the Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) trial.[14] In both trials, more than half of otherwise eligible patients with atrial fibrillation were excluded because they had relative or absolute contraindications to warfarin therapy, including bleeding disorders, coexisting medical disorders, alcoholism, and social and psychological reasons. The mean age of patients entered was 67 to 68 in four of the primary prevention trials[7,13-15] and 74 in a single trial.[6] Thus, the primary prevention trials entered a fairly rigorously screened and relatively young group of patients selected to have a low risk of bleeding on warfarin therapy. Even in these carefully selected patients receiving warfarin, 10% to 38% of patients were withdrawn from therapy during the trials.[6,7,11,13-15]

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• *What are the data in patients older than 75 with atrial fibrillation?*

More than half of the patients with atrial fibrillation are older than 75. The SPAF II trial separately randomly assigned 385 patients older than 75 to warfarin therapy (INR 2.0 to 4.5) versus an aspirin regimen of 325 mg per day. The primary event rate (ischemic stroke or systemic emboli) was 3.6% on warfarin therapy compared with 4.8% with the use of aspirin, which was not significantly different ($P = .40$). Because intracranial hemorrhage was much more common in the warfarin-treated group, the overall rate of stroke with residual effects was similar with both treatments (4.6% per year on warfarin versus 4.3% per year on aspirin). Thus, despite careful patient selection and monitoring of anticoagulation, the risks of bleeding, especially intracranial hemorrhage, were substantial in patients older than 75 and appeared to nullify any benefit of warfarin therapy relative to aspirin in this age group. Although it can be argued that the bleeding rate in this trial was high due to the relatively high INR (mean, 2.6), it is also likely that extending anticoagulation to less rigorously selected patients with less intensive monitoring would increase the bleeding risk. Lower-intensity therapy in this age group is currently being tested in the SPAF III trial.

• *What are the risks of anticoagulation?*

In the atrial fibrillation trials in which relatively younger, rigorously selected cohorts with a mean age of 67 to 68 were entered, the risk per year of major bleeding was 0.4%,[15] 1.3%,[14] 1.5%,[7] 1.7% (SPAF II <age 75),[16] and 2.5%.[13] The trials that entered older patients, however, had higher yearly rates of major bleeding on anticoagulation that were 2.8% in the EAFT (mean age, 72),[11] 3.2% in the AFASAK trial (mean age, 74),[6] and 4.2% in the SPAF II study (mean age, 80).[16] The relatively low complication rates in these closely monitored trials are probably not representative of those in more routine settings. It seems a certainty that if the entry criteria or monitoring had been less stringent, the bleeding risks would have been higher. Extrapolating low bleeding rates in younger patients to older patients is probably unwise, because the incidence of major bleeding increases with age, with one study estimating that the risk of major bleeding increased by 46% per decade above the age of 40.[17] Bleeding risk also increases with the intensity of anticoagulation as measured by the INR.[17] Perhaps the most feared complication is intracranial hemorrhage, an adverse event as dire as an embolic stroke. In SPAF II, intracranial hemorrhage occurred at a rate of 0.5% per year in the cohort younger than 75 but at 1.8% per year in the cohort older than 75.[16] Other studies have documented that the risk of intracranial hemorrhage goes up substantially with age.[18,19] In one study, the risk of intracranial hemorrhage was increased by 40% with each decade in patients receiving anticoagulants, such that the risk in an 80- to 90-year-old patient would be 5.4-fold greater than in a 30- to 40-year-old.[19]

• *Can patients with atrial fibrillation at a low risk of stroke be identified?*

There are several ways of identifying patients with atrial fibrillation at a low risk of stroke, defined as a risk of less than 1% per year. Such patients would reasonably be treated with only aspirin, or perhaps nothing. It is clear that patients younger than 60 years with lone atrial fibrillation have a low stroke risk of less than 0.5% per year.[5,20] Lone atrial fibrillation is variably defined, but a usable definition is atrial fibrillation in the absence of a history of stroke or TIA, diabetes mellitus, angina, heart failure, or myocardial infarction.[5] Above the age of 60, the risk of stroke in lone atrial fibrillation goes up, being 1.6% per year in 60- to 69-year-olds, 2.1% per year in 70- to 79-year-olds, and 3.0% per year in those 80 or older when untreated.[5] The SPAF I investigators identified 26% of the persons who had a stroke risk of only 1% per year on placebo; these low-risk subjects had no hypertension, no previous stroke or TIA, no recent heart failure, no global left ventricular dysfunction by echocardiogram, and a left atrium of 2.5 cm per m^2 or less. Similarly, in SPAF II, the stroke rate was only 0.5% per year in predefined low-risk patients treated with aspirin; low-risk patients were those younger than 75 without a history of hypertension, thromboembolism, or recent congestive heart failure. This low-risk group constituted 43% of the patients entered who were younger than 75.[16] The risks, expense, and inconvenience of lifelong warfarin therapy are not merited in low-risk patients.

• *Can patients with atrial fibrillation at a high risk of stroke be identified?*

Yes, high-risk groups can be identified who are probably more likely to benefit from taking warfarin. One group clearly is patients with a previous stroke or TIA as noted earlier. Other risk factors for stroke identified from multivariate analyses have been hypertension, diabetes mellitus, recent heart failure, left ventricular dysfunction by echocardiogram, and a left atrial size of more than 2.5 cm per m^2.[5,9,10]

• *What should we do until more data are in?*

Based on the foregoing, I would offer the following recommendations for antithrombotic therapy. Although these in many respects agree with those offered by Wipf,[1] I view the administration of aspirin as an acceptable therapy in more situations. First, patients with contraindications to taking warfarin should be treated with aspirin or possibly nothing if in a truly low-risk category. Contraindications to taking warfarin are common in patients with atrial fibrillation. In a recent Swedish study, it was estimated that only 26.5% of all patients with atrial fibrillation would be candidates for anticoagulation.[21] This figure is concordant with the high exclusion rates in the anticoagulant trials.[13,14] Second, groups identified as having a low stroke risk should also be given aspirin or nothing. Patients younger than 60 with lone atrial fibrillation are at a low risk, as are aspirin-treated patients younger than 75 without risk factors as defined earlier. Third, the

great majority of patients older than 75 should be treated with aspirin based on the results of SPAF II, because of the lack of proven superiority of warfarin and the clear increase in bleeding risk. Ongoing trials will provide further data about the relative risk and benefits of lower-intensity anticoagulation in this age group. Fourth, in patients of any age with previous TIA or stroke, the use of warfarin is preferred based on the results of EAFT. Fifth, among all other patients with atrial fibrillation (those younger than 75 without lone atrial fibrillation who have not had a stroke or TIA and who do not have contraindications to warfarin), either warfarin or aspirin therapy is reasonable, with the use of warfarin more effective but more difficult to administer and associated with a higher bleeding risk. Warfarin use should be particularly considered if any of the aforementioned risk factors are present.

Thus, despite the clear-cut efficacy of warfarin therapy in highly selected patients with atrial fibrillation in the published trials, in the real world of patients with atrial fibrillation, probably at least 50% of patients should be taking aspirin (or even nothing if truly low risk), either because they have an inherently low risk of stroke or because the bleeding risks of long-term warfarin therapy are unacceptable. Whether even lower intensities of warfarin therapy will prevent strokes with an acceptable bleeding risk remains to be seen.

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More on *Mycoplasma pneumoniae* Pneumonia

To the Editor: Chan and Welsh's and Cassell's recent comprehensive reviews of fulminant *Mycoplasma pneumoniae* pneumonia raised issues as to the pathogenesis of severe respiratory insufficiency and the value of corticosteroid therapy.[1,2] Our experience with a patient with *M pneumoniae* pneumonia invites further investigation of its molecular pathobiology and of the value of corticosteroid therapy.

Report of a Case

The patient, a 38-year-old female schoolteacher who did not smoke, had severe headache, fever, sore throat, nonproductive cough, and progressive dyspnea develop a week before hospital admission. Notably abnormal laboratory findings at the time of admission included a leukocyte count of 24×10^9 per liter (24,000 per mm^3) with a leftward shift; a platelet count of 120×10^9 per liter (120,000 per mm^3); a hemoglobin level of 98 grams per liter (9.8 grams per dl); and a hematocrit of 0.30 (30%). Serum sodium was 130 mmol per liter (130 mEq per liter); lactate dehydrogenase, 535 U; Po_2, 44.9 mm of mercury; Pco_2, 45.9 mm of mercury; and pH 7.35. A chest x-ray film showed bipulmonary acinar infiltrates. Antimicrobial therapy that was initiated consisted of intravenous vancomycin hydrochloride, 1 gram every 12 hours; aztreonam, 2 grams every 8 hours; metronidazole, 500 mg every 6 hours; erythromycin, 1 gram every 6 hours; and ribavirin, 33 mg per kg as a single loading dose, with 16 mg every 6 hours for 4 days and 8 mg per kg every 8 hours for 3 days. The ribavirin was added because of a recent exposure to rodents.

Despite the therapeutic regimen and 100% oxygen by mask, she continued to deteriorate, and intubation was necessary. Systemic vascular resistance ranged between 350 and 700 dynes per cm, the cardiac output from 6 to 8 liters per minute, and persistent hypotension required vasopressor support. Disseminated intravascular coagulation (DIC) supervened with a prolonged prothrombin time and partial thromboplastin time, increased fibrin-split products and D-dimer, and thrombocytopenia. Her arterial Po_2 was maintained with a fraction of inspired oxygen of 60% to 100% and positive end-expiratory pressure.

On the sixth hospital day, immunoglobulin (Ig) M antibodies to *M pneumoniae* were reported at 1:64 by immunofluorescence, and a test for IgG was negative. By this time, all sputum and blood cultures failed to yield a pathogen or were sterile, and serologic tests for *Legionella* and *Chlamydia* species, coccidioidomycosis, histoplasmosis, Q fever, influenza, parainfluenza, adenovirus, the human immunodeficiency virus, Sin Nombre, Puumala, and Hantaan viruses were negative or insubstantially present, and a purified-protein derivative (PPD) and urine test for *Legionella* species antigen were negative. A perfusion lung scan revealed a low likelihood of pulmonary emboli. All antimicrobial agents were discontinued, and the patient received intravenous doxycycline, 100 mg every 12 hours, and methylprednisolone sodium succinate, 60 mg every 12 hours.

The patient quickly became afebrile, her chest x-ray film showed improvement, the hemodynamic instability and DIC resolved, and the nasotracheal tube was removed four days later.

Discussion

We interpret these events to confirm the fulminant pneumonia as caused by *M pneumoniae* accompanied by hemodynamic and hematologic changes that closely resemble sepsis. We would postulate that a superantigen of *M pneumoniae*, as described by Cole for *Mycoplasma arthritidis*,[3] caused a massive T-cell proliferation and release of proinflammatory cytokines. These initiated the extensive pulmonary infiltrates and hemodynamic abnormalities noted in this patient. The dramatic response from corticosteroid therapy likely resulted from its T-lymphocytolytic properties by apoptosis.

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* * *

To the Editor: Chan and Welsh, in their recent review of fulminant *Mycoplasma pneumoniae* pneumonia, suggest that an enhanced host cellular immune response may account for the progression of illness in severely ill patients.[1] In addition, they comment that the use of systemic steroids "may be salutary." I present a case of severe *M pneumoniae* pneumonia that followed a biphasic course in which there was an initial response to antibiotics, but where the use of parenteral steroids ultimately proved to be lifesaving.

Report of a Case

The patient, a 41-year-old previously healthy female physician in active practice, was admitted to the hospital with dry cough, fever, and dehydration. Her illness had begun several weeks before admission when a dry cough developed in her and other family members. Her cough became productive 12 days before admission, and she had chills, malaise, and fever. The patient self-

medicated immediately with clarithromycin, 500 mg twice a day, inhaled steroids and bronchodilators. Within 48 hours, all symptoms resolved except the cough, which again became dry. Chest x-ray films showed a left upper lobe infiltrate. A PPD skin test was negative. She remained afebrile until the tenth day of medication, when she had chills, her cough worsened, and a fever of 38.3°C (101°F) developed. The next day, intravenous ceftriaxone sodium was administered. She was admitted to the hospital on day 12 of clarithromycin therapy with a fever to 40°C (104°F). She had recently traveled to an Arizona construction site, and she had many friends who had the acquired immunodeficiency syndrome (AIDS).

On admission the patient was coughing, had chills, and was requesting antipyretics. Her blood pressure was 100/60 mm of mercury, pulse rate 88 beats per minute, respirations 20 per minute, and temperature 40°C. Her leukocyte count was 7.4×10^9 per liter (7,400 per mm^3). A chest x-ray film showed an increase in left upper lobe infiltrates. The clarithromycin was stopped, and a regimen of intravenous erythromycin and cefuroxime was begun. A bronchoscopy showed inflammation and purulence in the left apical posterior bronchus. All stains and cultures of blood, sputum, and bronchoscopy specimens were negative for bacteria, virus, acid-fast bacilli, fungi, and *Chlamydia* and *Legionella* species, as were serologic tests of the same. Isoniazid, rifampin, pyrazinamide, and itraconazole were added on the second day of her hospital stay; however, her pulmonary function deteriorated, her fever escalated, her infiltrates progressed, and oxygen saturation fell into the 80s, so that by hospital day 7, pulmonary infiltrates were described as severe, multisegmental, and bilateral with pleural effusions. The patient had severe dyspnea at rest while receiving 100% fractional inspired oxygen; a Po_2 was 54 mm of mercury with the patient breathing room air.

An open-lung biopsy of the right lower lobe was done on the eighth hospital day. Microscopic studies revealed extensive bronchiolitis with pneumonia compatible with *M pneumoniae* pneumonia. Cold agglutinins returned positive at 1:128. Mycoplasma titers rose from 1:16 to 1:128. A course of parenteral steroids was begun on day 9. Her fever resolved immediately, and her shortness of breath resolved over the next 48 hours. Dramatic improvement was seen on her chest x-ray films within four days. A week later she was home without residual compromise of pulmonary function.

Discussion

Although conventional medical teaching conveys to us that illness caused by the microorganism *Mycoplasma pneumoniae* is mild, the literature is rife with reports of near-fatal and fatal cases of *M pneumoniae* pneumonia.[2-5] The diagnosis for as many as 20% of patients admitted to a hospital for community-acquired pneumonia may be *M pneumoniae* pneumonia.[6] The severity of illness has been attributed to a lack of timely administration of appropriate antibiotics.

The extrapulmonary complications of *M pneumoniae* pneumonia have been attributed to infection in those systems as well as to mechanisms of immune origin.[7] This case lends further support to an immune mechanism as the cause of "pulmonary complications" of *M pneumoniae* pneumonia and for the use of parenteral corticosteroids in the management of severe *M pneumoniae* pneumonia.

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Drs Chan and Welsh Respond

To the Editor: We thank Lawrence A. Cone, MD, DSc, and colleagues and Linda Dubins, MD, for reporting their cases of severe *Mycoplasma pneumoniae* pneumonia. Both patients, previously healthy and relatively young, improved only after the administration of corticosteroids. In addition, in the case reported by Dubins, progressive *M pneumoniae* pneumonia developed despite immediate treatment with clarithromycin. These findings are consistent with those of our patient and of the cases we reviewed.[1] Based on our arbitrary but strict criteria for respiratory failure in our review, the case presented by Dubins would not have been included in our series, despite the severe nature.

Cone and colleagues reported the case of a patient with respiratory failure and disseminated intravascular coagulation due to *M pneumoniae*. We agree that proinflammatory cytokines are probably involved in the exuberant, and possibly deleterious, inflammatory response. The mechanism of T-cell proliferation with proinflammatory cytokine release in response to a superantigen of *M pneumoniae* proposed by Cone and associates is certainly a possibility. We wonder, however, whether such a response, presumably due to the inflammatory Th1 cytokines interleukin (IL)-2 and gamma interferon, is in fact caused by a relative lack of anti-inflammatory cytokines IL-4 and IL-10 produced by Th2 cells. This hypothesis is indirectly supported by a report that showed that a low IL-10 response in sepsis is associated with an increased incidence of shock.[2] In trying to resolve this apparent paradox of the salutary effect of

anti-inflammation in host defense against microorganisms, our belief is that both an inflammatory response and then an anti-inflammatory "counterregulatory response" are required, but in a sequential fashion. Moreover, the Th2 cytokines are important mediators of the humoral arm of the specific immunity that we believe to be an important host defense mechanism against *M pneumoniae*.[1]

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Hereditary Hemochromatosis—Importance of Age and Sex?

To the Editor: The article by Yutaka Niihara, MD, and colleagues made interesting and informative reading.[1] The authors describe a unique case of hereditary hemochromatosis, which is the most frequently inherited disease in whites, seen in a 33-year-old woman. Typically, hemochromatosis becomes clinically manifest later in life and is seen more frequently in men than in women. In this context, we would like to draw your attention to another interesting case of a young woman found to have an early onset of symptoms associated with hemochromatosis.

Silva and co-workers report the case of a 26-year-old woman who for eight years had amenorrhea, cardiac failure, diabetes mellitus, and increased pigmentation of the skin, with biochemical markers of iron overload.[2] They emphasize that hemochromatosis must be excluded in all patients with unexplained cardiac failure. With early diagnosis and treatment, the life expectancy of such patients can be substantially prolonged.

Whereas perinatal or neonatal hemochromatosis is recognized as a distinct clinical disorder, Kaikov and associates report the cases of three asymptomatic siblings with hereditary hemochromatosis who had elevated serum iron levels, confirmed by hepatic biopsy studies.[3] Repeated phlebotomies resulted in a considerable decline of hepatic iron content. Hence, the diagnosis of hereditary hemochromatosis must be considered more frequently in children; regular phlebotomies may minimize organ dysfunction from iron overload in these patients.

Adams reviewed the cases of 57 families with hereditary hemochromatosis and found pronounced differences in iron overload among HLA-identical, sex-matched siblings.[4] Hence, the rate of iron accumulation may vary, and the extent of iron loading in hereditary hemochromatosis is not solely dependent on the duration of the disease.

These reports, in conjunction with Niihara and colleagues' case, reiterate that, regardless of a patient's age or sex, the diagnosis of hereditary hemochromatosis should be considered in patients with iron overload.

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* * *

Drs Niihara, Brouwer, and Cantos Respond

To the Editor: We would like to thank Abhay Anand, MD, and colleagues for their commentary and reminder of a recent report of a young woman with severe hemochromatosis.[1] That report, like ours,[2] stresses the importance of considering the diagnosis of hereditary hemochromatosis, regardless of age or sex, if certain clinical findings are present. Because iron deficiency is prevalent and its prevention is emphasized in our society, iron overload may easily be overlooked. It is our hope that these reports will increase awareness of the disease and improve the recognition and management of patients with hereditary hemochromatosis as well as their family members.

Finally, we would like to emphasize the importance of screening the family members of patients with hereditary hemochromatosis. Although this was not the focus of our recent report,[2] the importance of screening in this particular population cannot be overemphasized.

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More on the Prostate Cancer Screening Controversy

To the Editor: As expected, Michael Cher, MD, and Peter Carroll, MD, gave the urologists' view of the controversy surrounding prostate cancer screening.[1] I could handle the improperly defined term (length-time bias). I could even handle the selective use of statistics (they claim that about a quarter of the prostate cancers that will occur in the lives of 50-year-old men will be "clinically significant," but their reference points out that only 7% of the cases will be fatal[2]) and the fact that their recommendations run directly counter to the 1994 recommendations of the US Preventive Services Task Force.[3] It was their last paragraph, however, that shocked me into writing this letter.

Prostate cancer treatment has proven risks, the screening programs lack documented efficacy, and there is a tremendous psychological burden associated with being labeled as having an elevated prostate-specific antigen (PSA) level. Despite these factors, Drs Cher and Carroll "recommend that relatively young, healthy, asymptomatic men obtain a serum PSA assay" and then offer informed consent (that is, patient education of the risks and benefits of treatment) only after the positive results are known.

All patients should be counseled before obtaining a PSA level. To do anything less undermines our ultimate goal, the optimal care of our patients.

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* * *

Drs Cher and Carroll Respond

To the Editor: Theodore Ganiats, MD, incorrectly concludes that we do not provide informed consent regarding the risks and benefits of screening for prostate cancer (that is, obtaining a serum prostate-specific antigen [PSA] level in men visiting our office without signs or symptoms of prostate disease). In fact, the abstract clearly states, "men should be informed regarding the benefits and possible risks before being screened for prostate cancer." In the last paragraph of the article, we indeed said that we recommend to certain men visiting our clinic that they obtain a serum PSA test as a screen for prostate cancer. We feel that, as physicians, we have the right, and even the responsibility, to provide our patients with opinions and recommendations based on our review of the complex mass of available data. We anticipate that Dr Ganiats does the same, if he has clinical responsibilities.

We support decisions made by our patients with respect to all aspects of their care, including their decisions regarding screening for prostate cancer. The purpose of our article, in which we said that "there are no data to confirm that screening reduces morbidity and mortality" and "without these [data] the net benefit of screening cannot be calculated and predicted," was to provide the readers of The Western Journal of Medicine a timely review of the available data. We attempted to include the best information currently available on this subject. If Dr Ganiats has additional information, we would welcome his sending it to us. We hope that our review will allow practitioners to provide better informed consent, recommendations, and opinions to the men visiting their offices.

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Telephone Use and Costs in a Group Subspecialty Practice

To the Editor: Telephone communication is a major activity in physicians' offices, yet little study of this has been done. We analyzed our practice's phone use for the first three months of 1994, using software that allows for the collection of data on phone use. Our practice, a five-physician group, is limited to gastroenterology and serves a statewide referral base in New Mexico, using several satellite clinics.

We gathered information from three sources: our main office telephone system (Executone Integrated Digital System), cellular phones, and our answering service. Our system allows for extension-specific tracking of the number of calls and the duration of each call. Physician and nonphysician phone time could be distinguished and quantitated. Our phone system has no voice-mail component, and facsimile (fax) use was not tracked. All physicians also use radio pagers and mobile cellular phones. Calls to and from satellite offices, hospital wards, and homes could not be tracked. Because one of our physicians (on the average) was either at a satellite office or on a hospital ward, we assumed that the data we collected reflected the phone use of the equivalent of four of our five physicians.

Cost estimates were made, and phone bills, equipment costs, and nonphysician labor costs were tallied. For this analysis, we assumed that nonphysician employees require $10.50 per hour to cover salary and benefits. Omitted from the cost estimates were physician time, office space, and miscellaneous support for persons using the phone. The time preparing for calls, time between calls, and time required to be available for calls were not counted.

Our practice recorded 9,727 uses of the telephone per month, totaling 395 hours per month. The average call lasted 2 minutes, 26 seconds. Physicians' calls lasted about twice as long as nonphysician calls. Physicians talked 73 hours, 54 minutes per month (18 hours, 29 minutes per physician per month; 4 hours, 37 minutes per physician per week). There were wide variations in the length of conversation among the physicians. Insurance- and billing-related calls tended to be longer than appointment scheduling, procedure scheduling, and clinical data-gathering calls.

Telephone bills charged to our practice for all services were $2,062 per month, wage and benefit costs of nonphysician employees talking on the phone were $3,370 per month, and phone equipment depreciation was $370 per month. The total cost per physician per month was $1,160. After salaries, malpractice insurance, and rent, telephone-related costs were the fourth most costly budget item in the practice.

Our data confirm that telephone communication is a major part of the practice of medicine. Our cost estimates, which exclude physician time and staff time between calls, are substantial, yet probably low. Physicians should carefully analyze telephone and other office communication because inefficiencies can generate substantial unnecessary costs. Further study in a variety of practice settings is warranted. We also speculate that because so little data are available, telephone costs are underrepresented in the policy-making considerations of elected government officials, government regulators, and insurance companies. They are also poorly appreciated by patients and physicians themselves.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

One Evening

BRIAN THOMAS ANDREWS, MD, *San Francisco, California*

I sat finally at my cluttered desk, deeply fatigued after a long day in the operating room. My eyes fell randomly on an aging photograph of myself as an intern, and I recalled from distant memory that summer long ago when I began the practice of medicine. The newness of the MD degree was still with me then; my enthusiasm and respect for the art and practice of my profession were strong. I gazed at the photograph as evening approached, with deepening shadows cast on the walls of my office, and returned to the present to reflect on myself today.

I looked down at my tall stack of correspondence. At the top lay a letter from a law office on crisply formal linen stationery. It was a 90-day letter informing me that a patient intended to sue me for malpractice. I recalled the case well, a young man with a highly malignant brain tumor. After two recurrences of the tumor, I had not wanted to operate again. Despite my careful explanation of the risks, the family had demanded that everything possible be done, and now the young man lay paralyzed on one side and facing death. Of course there had been no malpractice here, but the young man and his family were embittered by the disease and life's cruelty, and I was the most obvious target of their anger. Ahead lay a long, arduous, expensive course of depositions, expert testimony, perhaps a trial, where the plaintiff's attorney would belittle my credentials and judgment, my care and treatment. This case, like others before, would be won. But there would be no victory, only despair.

Neurosurgery is a difficult field. I had always known that, always rationalized it, and always coped with it, by simply doing my best. But as I sat here now, the weight of so many ruined lives and dead patients bore down in the darkness.

I put this letter aside. Below this was a stack of "Explanation of Benefits" forms from medical insurance carriers. I glanced through these in silence, once again amazed that these companies could choose to pay what they wanted for my care and surgical skill and declare it the "usual and customary fee." And that amount is spiraling downward, out of my control, despite the fact that my own expenses of practice rise each year. The system is absurd, and as a result it is changing. What is replacing it seems just as absurd, pitting physician against physician under mounting administrative control and scrutiny of our decisions. Such "managed care" is often at the hands of those with little knowledge of my specialty and its complex nature and difficult decisions. They are there, it seems, to impede my doing needed tests and procedures.

I leafed through the rest of the mail. Near the bottom, a small letter in a red envelope with a handwritten address caught my eye. I opened it to find a card with a simple watercolor of a flower on the front. Inside was a note from the parents of a child I had treated a few months earlier. The little girl was 8 years old, an only child, who had slowly been getting dizzier and more unsteady, losing weight, and vomiting. Her pediatrician had been puzzled because she seemed neurologically and in every other way normal. Things went from bad to worse until her physicians in desperation took a magnetic resonance image of her brain and found a tumor the size of a lemon in her cerebellum. I saw the girl that very day. She was quiet, seemingly embarrassed by the commotion, as her parents tried to hide their anguish. The next day, after seven hours of tedious dissection using an operating microscope, I removed the tumor completely. Now she was cured and would live to grow, play baseball, and, I hoped, someday get married and have children of her own.

I gazed at the note of gratitude from the child's parents and reflected that there are many lessons in the practice of medicine today. Each lawsuit teaches humility, and each tragic result teaches respect for the terrible power of disease. The scrutiny of managed care, however irksome, casts no shadow if what we do is correct and justified. Each cure teaches respect once again for the science of medicine and the courage of our forebears to advance that science. The payment rendered in our profession is in large part not monetary, but reflected sometimes in children who grow up and play baseball. And in the darkness of the evening, I smile just a little.

(Andrews BT: One evening. West J Med 1995; 163:185)

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Lessons From the Practice

They Didn't Take Away My Pain, Did They?

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Brian died recently. He was an older, erudite, British-trained internist in my community. Relatively early in my career as a psychiatrist, he asked me to consult on a particularly problematic case. I was somewhat daunted by his patient's complaints about pain. Her symptoms had existed for years and were never able to be adequately alleviated by any physician's ministrations. She had had a particularly unhappy marriage, was now widowed, and lived alone in her modest home. She had been admitted to the hospital once again for a workup.

She was a small woman of Italian descent who in her conversation with me could not stray far from her preoccupation with her pain, her never-ending questions about it, and the requests for relief from her suffering. I could not make enough sense of her symptoms to reach a diagnosis and, like other physicians, felt unable to offer much help. All efforts to relieve her pain with medication had failed. I had given it a try myself, with similar results.

I told Brian I thought I had nothing new to offer this patient and should sign off. Despite that, he encouraged me to continue on the case, and so I did. (I wonder how Medicare would want me to code such a "service." It is probably not "covered" now in the days of micromanaged care.) In the meantime, a silent ovarian cancer was found, totally serendipitously. Mrs Gaboni's pain symptoms had no anatomic relationship to this disease.

Mrs Gaboni was now hopeful that a surgical procedure would relieve her of her distress. She was not overly fearful of the upcoming operation.

I was lucky enough to see her immediately after the surgical procedure, when not enough time had passed for the mental effects of the anesthesia to have fully receded. After alerting her to my presence and the fact that the procedure was over, I saw a horrified look cross her face. With great apprehension and urgency, she asked, "They didn't take away my pain, did they?" I had enough presence of mind to quickly reassure her that only the cancer had been removed and that from what I had just learned about her "condition," the pain had not been touched. Right before my eyes, she gradually returned to her previous state of mind, saying, "Doctor, can't you do something about this pain? I still have it."

At that moment, I learned from Mrs Gaboni something very important about human pain and suffering. I could now make sense of not only her symptoms, but also of the "condition." I had my diagnosis and could formulate a plan of what to do and, equally important, what not to do. This lesson has stood me in good clinical stead now for many years in the care of patients. Thank you, Brian. Thank you, Mrs Gaboni.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Dillon OS: They didn't take away my pain, did they? West J Med 1995; 163:186)

Dr Dillon is in private practice in psychiatry in Berkeley, California.
Reprint requests to O'Neil S. Dillon, MD, 891 Regal Rd, Berkeley, CA 94708.

THE WESTERN JOURNAL OF MEDICINE

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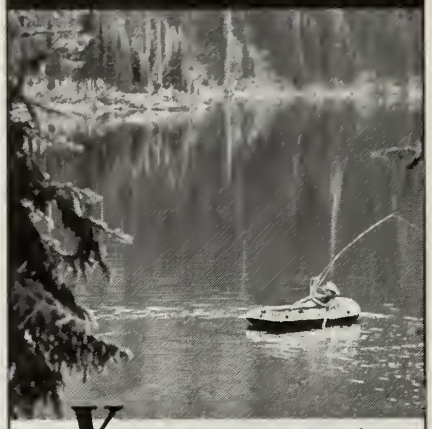

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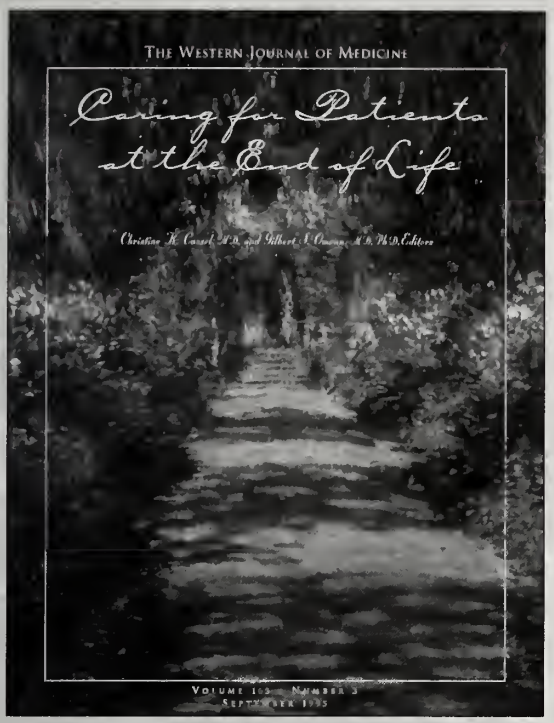

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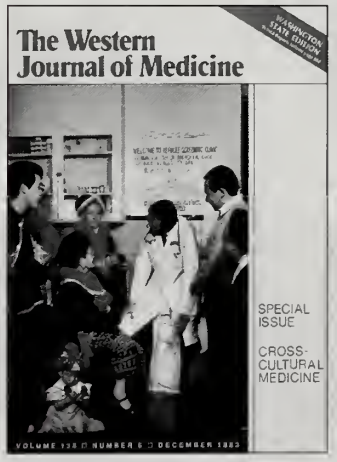

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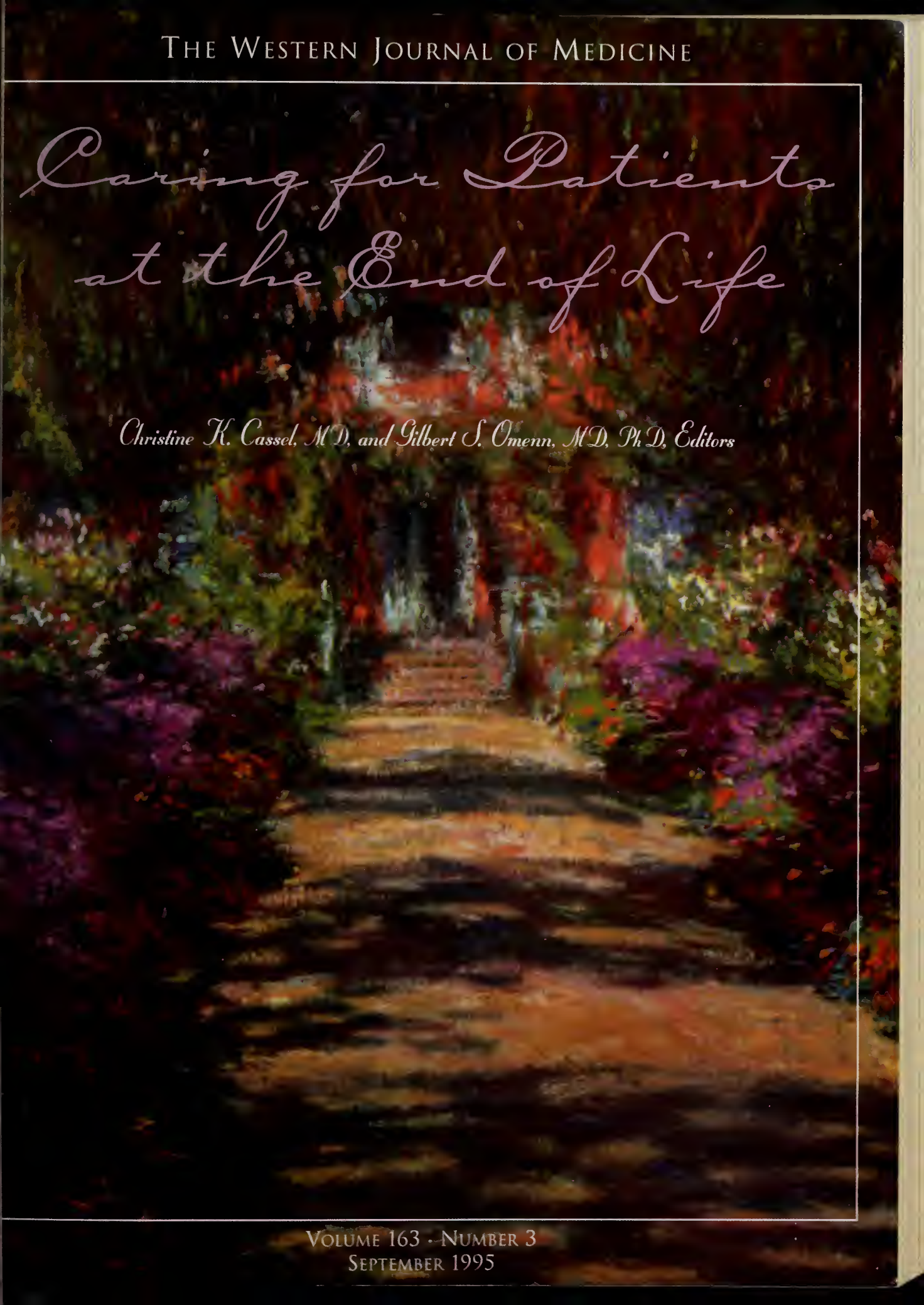

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The Western Journal of Medicine

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Caring for Patients at the End of Life

CHRISTINE K. CASSEL, MD, and GILBERT S. OMENN, MD, PhD, Special Editors

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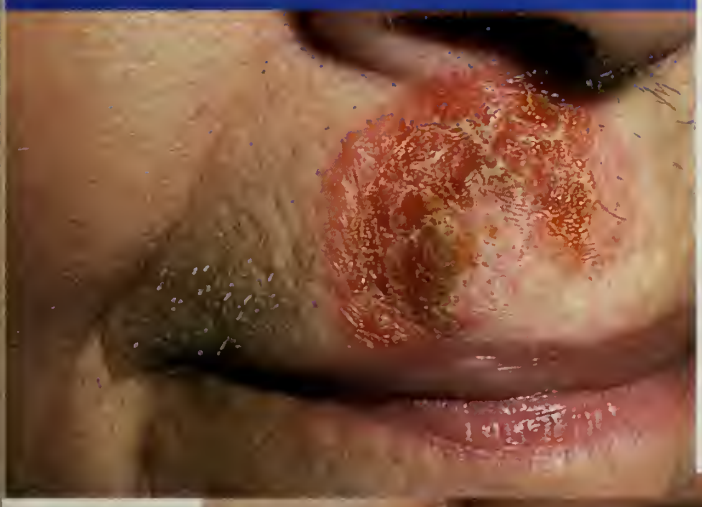

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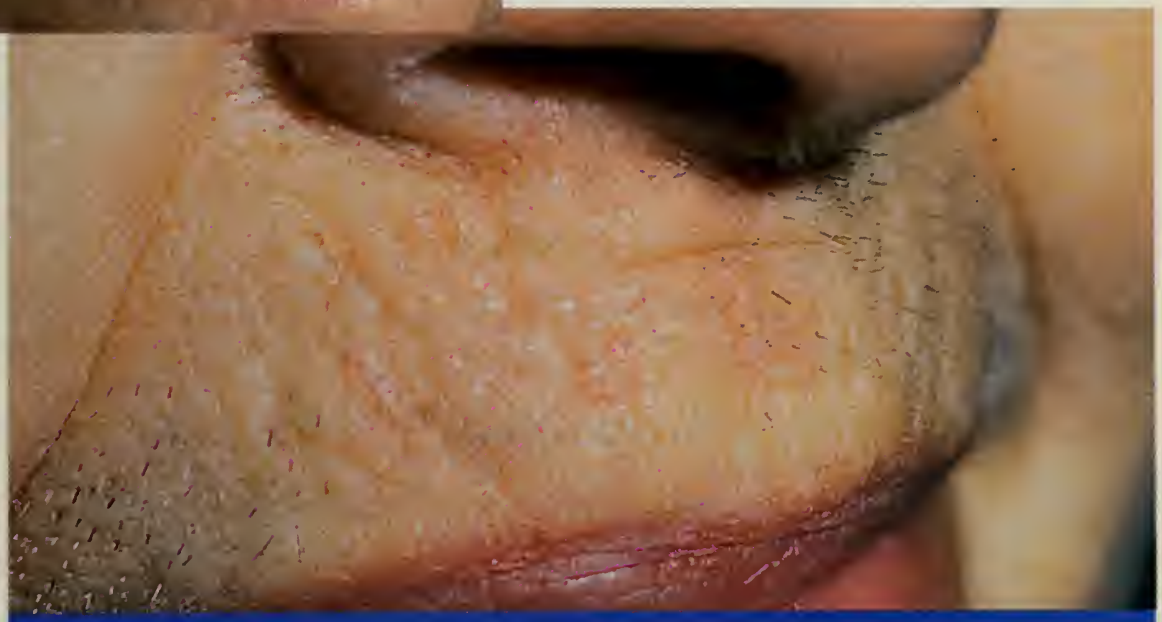

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1. Britton JW, Fajardo JE, Krafte-Jacobs B. Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr.* 1990;117:827-829.
2. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. *Pediatrics.* 1992;89:210-214.
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(Continued from Page 200)

(Continued on Page 206)

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October 27-28—**Ethics in Managed Care Conference.** Samaritan Health Services at the Buttes Hotel, Phoenix. Fri-Sat. Contact: Linda Luzader, (602) 495-4936.

October 27-29—**Arizona Orthopaedic Society—Scientific Meeting**. Maricopa Medical Center at Westin La Paloma, Tucson. Fri-Sun. Contact: Patrice Hand, (602) 246-8901.

November 1-4—**AMTA Methadone Conference**. University of Arizona College of Medicine at The Pointe Hilton, Phoenix. Wed-Sat. Contact: U of A.

November 2-4—**Eighth Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 2-5—**24th Annual Alex Newman Radiology Conference: Abdominal Imaging and MRI**. Maricopa Medical Center at the Camelback Inn, Scottsdale. Thurs-Sun. Contact: (602) 267-5366.

November 4—**Audiology Videoconference**. Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 4—**Recent Developments in Mood Disorders**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Sat. Contact: U of A.

November 5—**Career Choices.** American College of Physician Executives at the Westin La Paloma, Tucson. Sun. Contact: (800) 562-8088.

November 5-10—1995 **Annual Meeting, American Urological Association, Western Section.** Phoenician Resort, Scottsdale. Sun-Fri. Contact: (714) 898-9155.

Noveber 6-10—**Physician in Management Seminar I.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 6-10—**Physician in Management Seminar II.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 16-19—**Controversies in Critical Care**. Society of Critical Care Medicine at the Pointe Hilton Resort on South Mountain, Phoenix. Thurs-Sun. Contact: (714) 282-6000.

November 17—**Arthritis Update.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Fri. Contact: U of A.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 18-19—**Workshop on Transesophageal Echocardiology.** American Society of Anesthesiologists at the Marriott's Camelback Inn, Scottsdale. Sat-Sun. Contact: (708) 825-5586.

December 2—**ENT for the Specialist**. Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 12-16—**5th Annual Psychopharmacology Review**. University of Arizona College of Medicine at the Westin La Paloma Resort. Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 30—**Contemporary Management of Sinusitis**. UCSF at Laurel Heights Auditorium, San Francisco. Sat. Contact: UCSF.CME Listing - August 1995

January 30-February 3— **34th Annual Scientific Session of the Western Society of Allergy and Immunology**. Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, P.O. Box 1122, Roanoke, TX 76262. (817) 491-2616.

ANESTHESIOLOGY

October 29-November 4—**Hawaiian Seminar on Clinical Anesthesia**. California Society of Anesthesiologists at Hyatt Regency Poipu Beach, Kauai, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

November 3-5—**Anesthesiology Update: 1995**. UCD at Monterey Plaza, Monterey. Fri-Sun. 12 hrs. $300. Contact: UCD.

January 10-13—**UCSD Anesthesia Update**. UCSD at Hotel del Coronado. Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 11-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. 2 wks. 20 hrs. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City, CA 94404. (800) 345-3691.

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 26-29—**5th John J. Bonica Hawaii Pain Conference**. Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

November 18—**14th Annual Sharrer Symposium: Progress in Cardiology**. Kaweah Delta Hospital District at Visalia Convention Center. Sat. 6 hrs. Contact: Barbara Porter, RN, (209) 625-7106.

December 9—**Cardiac Therapeutics.** USC at Ritz-Carlton, Laguna Niguel. Sat. 8 hrs. $75. Contact: USC.

DERMATOLOGY

October 14-15—**The Skin from A to Z.** UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

October 13-15—**Advances in Emergency Medicine.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 210)

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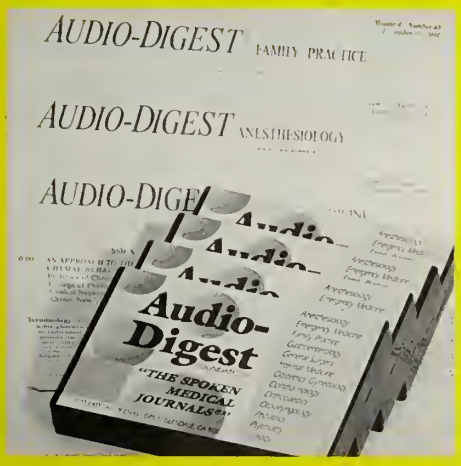

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- ☐ GENERAL SURGERY
- ☐ INTERNAL MEDICINE
- ☐ OBSTETRICS/GYNECOLOGY
- ☐ OPHTHALMOLOGY
- ☐ *ORTHOPAEDICS
- ☐ OTOLARYNGOLOGY—Head and Neck Surgery
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CONTINUING MEDICAL EDUCATION

(Continued from Page 208)

October 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 30-November 3—**24th Annual Topics in Emergency Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

November 11-12—**Biomechanics of Trauma.** UCSD at Le Meridien Coronado. Sat-Sun. 11 hrs. $200. Contact: UCSD.

November 13-17—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 3-8—**16th Annual Current Concepts in Emergency Care**. American College of Emergency Physicians at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269.

December 11-15—**Emergency Medicine Symposium II**. UCSD at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 18-20—**California Trauma Conference**. UCD at Hyatt Regency, Sacramento. Thurs-Sat. 17 hrs. $425. Contact: UCD.

February 24-March 2—**Pediatric Emergencies**. UCSD at Royal Lahaina, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

October 11-13—**10th Annual Primary Care Medicine: Principles and Practice.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 20 hrs. $495. Contact: UCSF.

October 14— **Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Radisson Hotel, Sacramento. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

October 16-18—**Neurology and Outpatient Psychiatry for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 25-28—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

October 26-29—**Nevada Academy of Family Physicians.** NAFP at Tropicana Hotel, Las Vegas, Nevada. Thurs-Sun. 21 hrs. Contact: Barbara Bollin, NAFP, P O Box 27713, Las Vegas, NV, 89126-1713. (702) 647-0117.

November 6-8—**Geriatrics Update 1995**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

December 7-9—**Clinical Care of the AIDS Patient**. UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 24 hrs. $395. Contact: UCSF.

January 20-27—**Sports Medicine.** UCSD at Royal Waikoloan, Kona, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

February 1-3—**Neurology for the Non-Neurologists.** UCSD. Thurs-Sat. 21 hrs. $500. Contact: UCSD.

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

INFECTIOUS DISEASE

November 3-5—**Advances in Infectious Disease**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

November 3-4—**6th Annual Practical Methods of Diabetes Management**. MMC/UCI Center for Health Education at Sutton Place Hotel, Newport Beach. Fri-Sat. Contact:Center for Health Education, (310) 933-3811.

November 10-11—**American College of Physicians: Northern California Regional Scientific Meeting**. American College of Physicians at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 11 hrs. $150-$170. Contact: Carol Finley, St Mary's Medical Center, (415) 750-5955.

MANAGED CARE

October 5-7—**Doctors in Distress II.** American College of Legal Medicine at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 17.25 hrs. Contact: ACLM, 611 E Wells St, Milwaukee, WI 53202. (414) 276-1881.

NEPHROLOGY

November 9-10—**International Symposium on Continuous Renal Replacement Therapy.** UCSD. Thurs-Fri. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

October 15—**OB/GYN Pathology**. USC at Red Lion Hotel, Glendale. Sun. 6 hrs. $175. Contact: USC.

October 16-20—**OB/GYN Review**. USC at Red Lion Hotel, Glendale. Mon-Fri. 38 hrs. $640. Contact: USC.

October 23-28—**18th Annual Review Course in Clinical Obstetrics and Gynecology**. Memorial Medical Center/UCI Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Mon-Sat. Contact: MMC/UCI. (310) 933-3811.

November 10-12—**Current Issues in Perinatal Medicine**. MMC/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Fri-Sun. Contact: Center for Health Education, (310) 933-3811.

December 1-2—**Controversies in Hormones, Menopause and Breast Cancer**. MMI/UCI Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

December 7-10—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's, Las Vegas. Thurs-Sun. $295. Contact: Center for Continuing Medical Education, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

February 10-13—**51st Annual Postgraduate OB/GYN Assembly**. Obsterical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Sat-Tues. 22 hrs. Contact: Director, 5820 Wilshire Blvd #500, Los Angeles 90036. (213) 937-5514.

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

October 23-27—**Occupational and Environmental Medicine V**. UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

OPHTHALMOLOGY

November 18—**Diabetes and the Eye**. MMI/UCI Center for Health Education at Long Beach Memorial Medical Center. Sat. Contact: Center for Health Education, (310) 933-3811.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists.** Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, P O Box 1216, Murrieta, CA 92564. (909) 677-4482.

ORTHOPEDICS

November 9-11—**Integrated Function of the Lumbar Spine and Sacroiliac Joints.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 15 hrs. $335. Contact: UCSD.

November 30-December 1—**Disorders of the Upper Extremities.** UCSF at Miyako Hotel, San Francisco. Thurs-Fri. 12 hrs. $375. Contact: UCSF.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Educaton Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 825-6774.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.

(Continued on Page 212)

HOSPICE:

Dynamic Foundations, Dynamic Futures

The National Hospice Organization,
The Annenberg Center at Eisenhower,
and
The Council of Hospice Professionals
present

The 17th Annual
Symposium and Exposition
Where: **The Phoenix Civic Plaza**
Phoenix, Arizona
When: **November 4 – 8, 1995**

Physicians are taught to prevent death at any cost. But when the diagnosis is terminal, it is important for patients and families to know that their doctor can offer them care beyond a cure. Hospice, a team-delivered program of care, offers physicians a good, sound solution to their most difficult patients—those facing death. It carves out a meaningful role for the physician as part of the hospice team controlling their patients' symptoms and easing their pain—physical, emotional and spiritual.

- Author series with recently published authorities on end of life issues
- An exposition of hospice products and services
- Networking opportunity with 2,000 professionals from around the country
- CME- and CEU-accredited educational tracts in each of the following areas:
  - Access to care
  - AIDS care
  - Ethical issues
  - Grief
  - Pain
  - Pediatric issues
  - Rural issues
  - Spiritual care

Please contact the National Hospice Organization at (703)243-5900 to receive information on conference registration and planning.

Founded in 1978, NHO is a nonprofit, public benefit, charitable organization advocating for the needs of terminally ill persons in America. It is the only nonprofit membership organization devoted exclusively to the promotion of hospice care.

(Continued from Page 210)

OTOLARYNGOLOGY

October 15-20, November 12-17—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 2-4—**San Francisco Otology-Neurotology—1995**. UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 22 hrs. $425. Contact: UCSF.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists**. Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, P O Box 1216, Murrieta, CA 92564. (909) 677-4482.

PATHOLOGY

November 3-5—**45th Annual Meeting of the National Kidney Foundation.** California Convention Center, San Diego. Fri-Sun. 17 hrs. Contact: NKF, 30 E 33rd St, New York, NY 10016. (800) 622-9010.

November 10-11—**Pathophysiology and Treatment of Gastroesophageal Reflux.** USC at at Health Sciences Campus. Fri-Sat. 16 hrs. Contact: USC.

PEDIATRICS

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 19-21—**Practical Pediatric Electrophysiology and Pacing Course.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. Contact: Children's Hospital and Health Center, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 22-26—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital and Health Center at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. Contact: Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 26-28—**34th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15hrs. $295. Contact: David Steward, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 1-3—**Current Concepts in Pediatric Medicine**. Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego, CA 92123. (619) 576-4072.

PLASTIC SURGERY

November 4-5—**Endoscopic Plastic Surgery and Beyond**. UCSD. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

November 11-14—**Surgical Advances in Cleft and Cleft Palate.** UCD at Monterey Plaza. Sat-Tues. 18 hrs. $450. Contact: UCD.

December 8-9—**2nd Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources. Fri-Sat. Contact: Martin Borsanyi, c/o Professional Image, (714) 760-1522.

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face**. UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

October 6 - April 4—**Evenings with the Masters**. Northern California Group Psychotherapy Society at Northern California Locations. Fridays. 2-3 hrs. $10. Contact: Ann Steiner, Ph.D., 821 E Second St, #203, Benicia 94510. (707) 745-6225.

October 13—**7th Annual Law Day: Youth, Violence and the Community-A Psychosocial Perspective.** Napa State Hospital at Rehabilitation Center Auditorium, Napa. Fri. 5 hrs. Contact: Napa State Hospital, (707) 253-5728.

November 3-5—**41st Annual Group Therapy Symposium**. UCSF. Fri-Sun. Contact: UCSF.

February 11-13—**29th Annual Recent Advances in Neurology**. UCSF at Ritz-Carlton, San Francisco. Sun-Tues. Contact: UCSF.

PULMONARY/CRITICAL CARE

October 19-21—**14th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 17 hrs. $430. Contact: UCSF.

December 1-2—**Laser Bronchoscopy, Stents, Brachytherapy, Thoracoscopy for the Pulmonologist and Emphysema Surgery.** MMC/UCI Center for Health Education at Long Beach Memorial Medical Center. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

RADIOLOGY

October 21-22—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. 13 hrs. $375. Contact: UCSD.

October 22-23—**Neuroradiology Update**. UCSD at Sheraton Grande Torrey Pines, La Jolla. Sun-Mon. 13 hrs. $375. Contact: UCSD.

October 23-27—**20th Annual San Diego Postgraduate Radiology Course**. UCSD at Hotel del Coronado. Mon-Fri. 27 hrs. $575. Contact: UCSD.

October 27-28—**15th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado. Fri-Sat. 14 hrs. $375. Contact: UCSD.

November 2-4—**8th Annual Obstetrical and Transvaginal Ultrasound Course—A Hands-On Course.** MMC/UCI Center for Health Education at Doubletree Hotel, Orange. Thurs-Sat. Contact: Center for Health Education, (310) 933-3811.

January 28-February 4—**Multispecialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest Ultrasound and Bone.** UCSD at Hotel del Coronado, San Diego. 1 wk. 40 hrs. Contact: UCSD.

March 10-15—**Neuro and Musculoskeletal MR.** UCSD at Hotel del Coronado, San Diego. Sun- Fri. 28 hrs. $425-$625. Contact: UCSD.

SURGERY

December 1-3—**International Symposium on TMJ Arthroscopy and Arthroscopic Surgery**. Fri-Sun. $695. Contact: Peg Hoelderlin, c/o Professional Image, (714) 760-1522.

January 12-13—**What's New In General Surgery: 18th Annual Postgraduate Course.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $285. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

October 7—**Multi-Cultural Diversity in Health Care Symposium**. UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

December 23-29—**Advances in Medicine 1995**. Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Fri. 6 hrs. $475. Contact: Symposium Maui, PO Box 10185, Lahaina, HI 96761. (808) 661-8032.

January 17-20—**Medicine Meets Virtual Reality 4: Health Care in the Information Age—Future Tools for Transforming Medicine**. UCSD at San Diego Convention Center. Wed-Sat. 23 hrs. $450. Contact: UCSD.

February 19-23—**Physician Heal Thyself**. UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 28-29—**Informatics Fair '95: Computers in Medicine.** Denver Medical Library at Presbyterian/ St Luke's Hospital. Contact: Denver Medical Library, (303) 839-6670.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

(Continued on Page 216)

In the battle against allergic rhinitis

A FIRST LINE OF DEFENSE

Symptomatic relief superior to QD non-sedating antihistamines[1,2]

See charts on reverse side

QD staying power

Convenient once-daily dosing for better compliance

Onset of action as early as 12 hours[3]

Maximum benefit is generally seen within 3 to 4 days[3]

Excellent safety profile

No measurable effect on HPA function at recommended doses[4,5]

The most commonly reported side effects are headache and nasal irritation, each with an incidence comparable to placebo

ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Please see brief summary of prescribing information on following page.

ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g. joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7 and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
COLLEGEVILLE, PA 19426

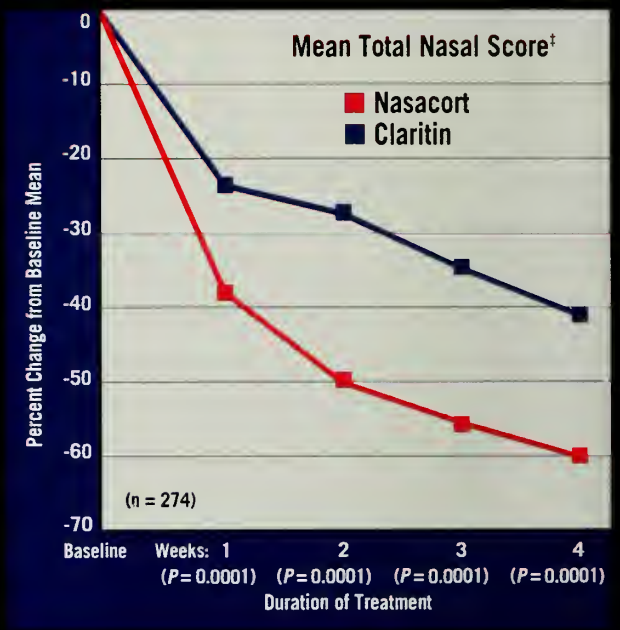
Innovators in Respiratory Care

NA06L795(8350)C 7/95 FC#95-J702

Printed in U.S.A.

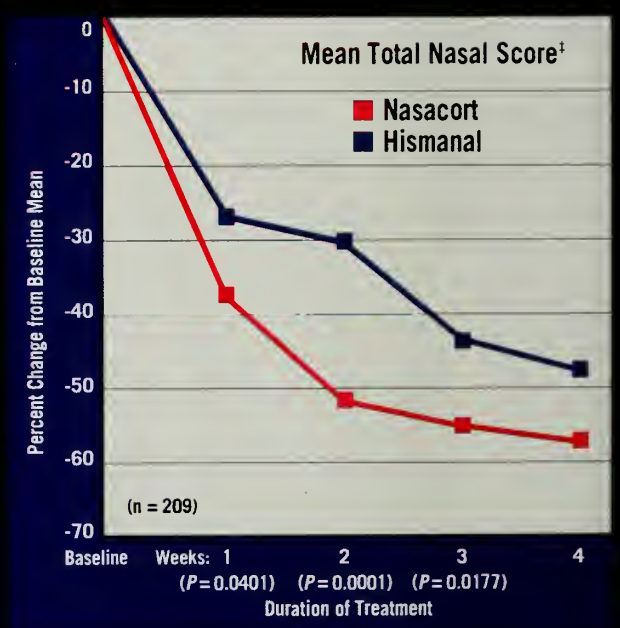
Superior symptomatic relief vs. QD non-sedating antihistamines[1,2]

NASACORT VS. CLARITIN[1]*



‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[2]†



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*

† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*

§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

REFERENCES

1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

CONTINUING MEDICAL EDUCATION

(Continued from Page 212)

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 7-8—**Pediatrics for the Practitioner—Back to the Basics.** New Mexico Pediatric Society at the Roswell Inn, Roswell. Sat-Sun. Contact: Steve Yabek, MD, NM Pediatric Society, 715 Grand Ave NE, Ste 207, Albuquerque 98102. (505) 848-3700.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

October 20-21*—**ECG, Interpretation for the Primary Care Physician.** New Mexico Heart Institute at the Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, NM Heart Institute, 1001 Coal SE, Albuquerque 87106. (505) 841-1001 or (800) 888-6642.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic Scottsdale, 13400 E Shea Blvd, Scottsdale 85259. Phone, (602) 301-7447; fax (602) 301-8323.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting.** Santa Fe. Fri-Sat.. Contact: Billie Dytzel, (505) 265-0732.

February 24-25—**Mammography: Practical Challenges of the 90s for the Technologist.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax, (404) 552-9859.

*Corrected date

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

October 27-29—**Intensive Interactive Head and Neck Imaging Course.** University of Utah at Marriott Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions.** Park City. Contact: UUMS.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of PCE, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

(Continued on Page 218)

The American College of Legal Medicine
in Cooperation with
The California Medical Association
presents

Doctors in Distress II

Medical Legal Issues: The Era of Managed Care and Escalating Physician Discipline

October 5-7, 1995
San Diego Hilton Beach and Tennis Resort
San Diego, California

ACLM's two-day conference covers medical-legal and ethical issues of Managed Care, Peer Review, and Professional Licensing and Discipline. This conference has been approved for up to 17.25 Category I CME credit hours.

A variety of recreational activities are also available for the entire family. The San Diego Hilton has its own health and tennis club, recreational area and a private dock with available sailboat, catamaran and Aqua Cycle rentals. Located nearby is Sea World and the Balboa Park Zoo Museum.

To receive more information, call or write to:
The American College of Legal Medicine
611 East Wells Street
Milwaukee, WI 53202
800/433-9137

APS/SPR/APA ANNUAL MEETING

Announces A New Name

In recognition of the comprehensive nature and content of our annual meeting which encompasses all aspects of the disciplines of Pediatrics, and to recognize the pediatric subspecialty groups that meet with us, the American Pediatric Society (APS), Society for Pediatric Research (SPR) and Ambulatory Pediatric Association (APA) announce a new name for the annual meetings.

PEDIATRIC ACADEMIC SOCIETIES' ANNUAL MEETING

Please join us for the 1996 Pediatric Academic Societies' Annual Meeting in Washington, D.C., May 6-10 (Monday - Friday) at the Sheraton Washington and Omni Shoreham Hotels.

CALL FOR ABSTRACT SUBMISSIONS

The deadline is JANUARY 4, 1996.

APS/SPR Abstract and Program Information:
141 Northwest Point Blvd., P.O. Box 675, Elk Grove Village, IL 60009-0675, Tel: (708)427-0205, Fax: (708) 427-1305.

APA Abstract and Program Information:
6728 Old McLean Village Drive, McLean, VA 22101, Tel: (703)556-9222, Fax: (703)556-8729, E-Mail: ambpeds @ aol.com

Report on Financing of Practice Acquisitions

HPSC Financial Services has provided the financing for the acquisition of practices whose selling prices are shown below.

State/Selling Price	State/Selling Price	State/Selling Price
AZ...$300,000	GA ..$106,000	NH....$25,000
CA 50,000	ID 225,000	NC....120,000
CA 128,000	LA.....185,000	NC....283,000
CA 90,000	LA.....129,000	NC....125,000
CA 120,000	MA....125,000	NM ...160,000
CO....110,000	MA....248,679	NV 64,795
FL.....125,000	MA.....68,000	NY 100,000
FL.....90,000	MA.....65,000	NY 400,000
FL.....100,000	MA....235,000	NY 165,000
FL.....135,000	MA.....80,000	PA.....145,000
FL.....290,000	MA....200,000	TX.....90,000
FL.....275,000	MA....260,000	TX.....150,000
FL.....55,000	MA....225,000	TX.....150,000
FL.....270,000	ME.....40,000	VA.....94,950
FL.....198,000	MI.....365,000	VA.....300,000
FL.....240,000	MI.....45,000	VA.....15,000
GA 329,000	MI.....150,000	VT.....165,000
GA 150,000	MO ...300,000	WA....151,805
GA 298,000	MO ...395,500	

Selling, expanding, acquiring a practice? HPSC, which has financed over 60,000 doctors since 1975, offers you all these benefits:

1. Financing of practice acquisitions, up to 100% of purchase price. Competitive fixed rates – no "points" or hidden fees.
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3. For start-ups and expanding practices, we finance equipment, leasehold improvements, working capital, merchandise contracts, computers, and other office equipment.
4. Innovative, flexible custom plans, geared to cash flow; tax benefits.
5. Leasing options: deferred payment; no down payment; graduated payments up to 72 months.
6. Quick response: up to $125,000, 1 hour. Over $125,000, with all requested documents in place, 24-48 hours.
7. Easy add-on to existing lease as practice grows.
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Would you like to discuss your project, or get more information?
Call us at 1-800-225-2488 or fax 1-800-526-0259.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 216)

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 22-23—**Laparoscopic Surgery: Upper GI**. Seattle. Fri-Sat. Contact: U/W.

September 25-29—**Respiratory Protection.** Anchorage. Tues-Sat. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

September 28—**Infectious Disease Conference.** Renton. Thurs. Contact: Valley Medical Center, (206) 575-4721.

September 29-30—**Topics in Internal Medicine**. Seattle. Fri-Sat. Contact: VMMC.

September 29-30—**Breast Cancer Update**. Seattle. Fri-Sat. Contact: U/W.

October 5-6—**ACLS.** Seattle. Thurs-Fri. Contact: VMMC.

October 6—**John Locke Cardiology.** Seattle. Fri. Contact: Swedish, (206) 386-2265.

October 6—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

October 6-7—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Fri-Sat. Contact: U/W.

October 11—**Infectious Disease Update**. Northwest Hospital, Seattle. 4 hrs. Contact: Educational Services, Northwest Hospital, (206) 368-1623.

October 11—**Complex Chemical Exposures: Soft Data, Hard Issues.** Portland. Wed. Contact: Center for Occupational Health and Safety, (206) 543-1069.

October 21—**Practical Pediatrics.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

October 21-22—**ACLS**. Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

October 25—**The Changing Workplace: Effective Measures to Cope With Job Stress.** Seattle. Wed. Contact: Center for Occupational Health and Safety, (206) 543-1069.

(Continued on Page 219)

CONTINUING MEDICAL EDUCATION

(Continued from Page 218)

October 26-27—**Current Concepts in Drug Therapy**. Seattle. Thurs-Fri. Contact: U/W.

October 27—**7th Annual Current Concepts in Perinatology**. Tacoma. Fri. Contact: Multicare, (206) 552-1221.

October 27-28—**Mental Health Update: Training in...**Seattle. Fri-Sat. Contact: U/W.

November 2-3—**Ergonomics of Occupational Hand-Arm and Whole-Body Vibration.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 3—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

November 8—**Pain Management.** Northwest Hospital, Seattle. 4 hrs. Contact: Educational Services, Northwest Hospital, (206) 368-1623.

November 10-11—**6th Annual Regional Conference for Occupational Therapy and Physical Therapy.** Seattle. Fri-Sat. Contact: U/W.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

Novembr 13—**New Ways of Organizing Data: Geographical Information Systems.** Seattle. Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 16-18—**Surgery Update**. Seattle. Thurs-Sat. Contact: U/W.

November 17—**Pinkham Basic Science Lectureship**. Seattle. Fri. Contact: Swedish, (206) 386-2265.

November 24—**Urology Update.** Seattle. Fri. Contact: VMMC.

November 30—**Air Pollution: Has Particulate Matter Increased Mortality? Lessons From Seattle and Spokane**. Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 1—**Pediatrics Update**. Seattle. Fri. Contact: VMMC.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9—**Fiberoptic Intubation**. Seattle. Sat. Contact: U/W.

December 14—**Clinical Recognition of Health Hazards in the Home.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety.

December 14-16—**Primary Care for the Ob/Gyn**. Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference**. Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

January 11-12—**Ergonomics.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 20—**Pharmacology Update**. Seattle. Sat. Contact: Swedish Hospital, (206) 386-2265.

January 25—**Ethical Issues in Occupational Health**. Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

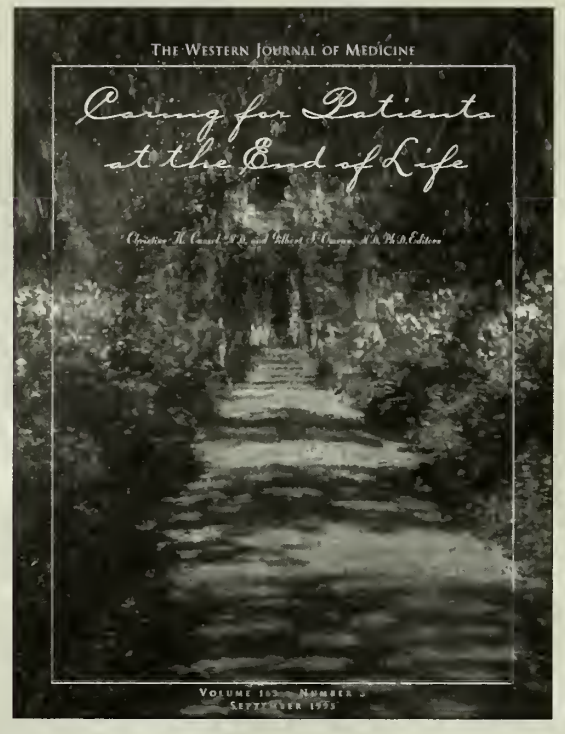
U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.



CARING FOR PATIENTS AT THE END OF LIFE

Articles Include:

- The Social and Cultural Context of Dying
- Patient Perspectives on Dying
- Cross-Cultural Dimensions in Dying and Death
- Care of Children Who Are Dying
- Ethical Dilemmas in the Care of Dying Patients
- Management of the Dying Patient
- The Futility Problem
- Decision-making in the Managed Care Context
- Religious Dimensions of Dying and Death
- Care of the Family When the Patient is Dying

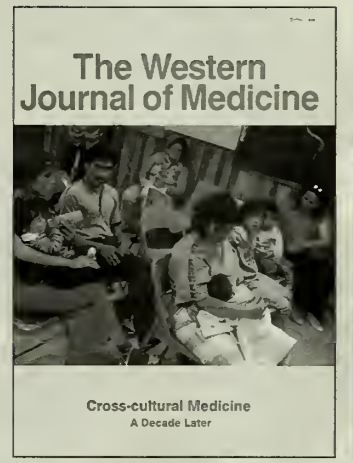
Christine Cassel, MD, & Gilbert S. Omenn, MD, PhD
Special Issue Editors, 1995

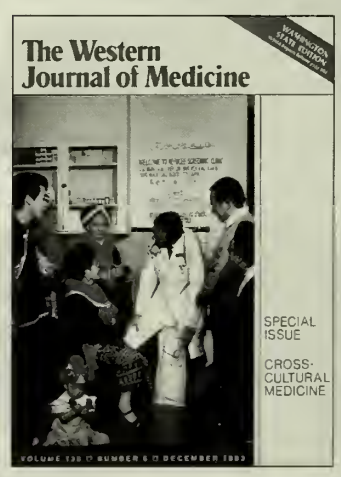
Cross-cultural Medicine —A Decade Later

Ethnic Groups Covered

Chinese-American, East Indian, Afghan, Gypsy, American Indian, Vietnamese, African American, Iranian, Korean American, Laotian, Ethiopian, Russian, Migrant Workers, and French

Judith Barker, PhD
Special Issue Editor, 1992





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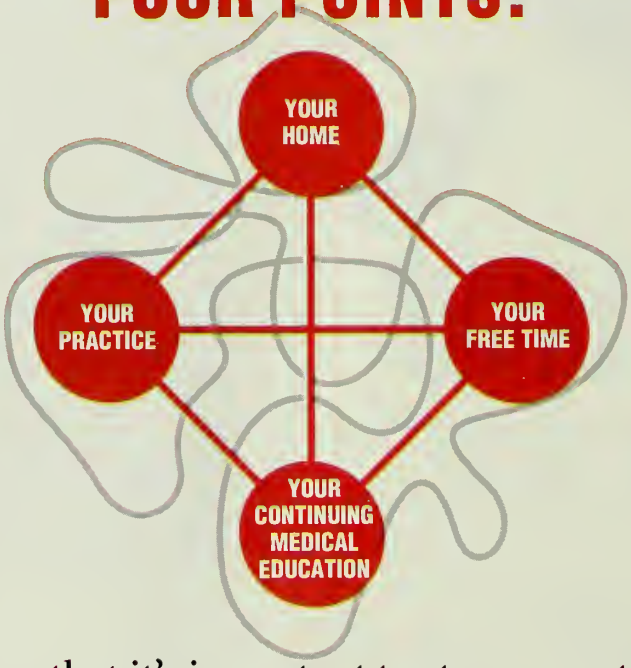

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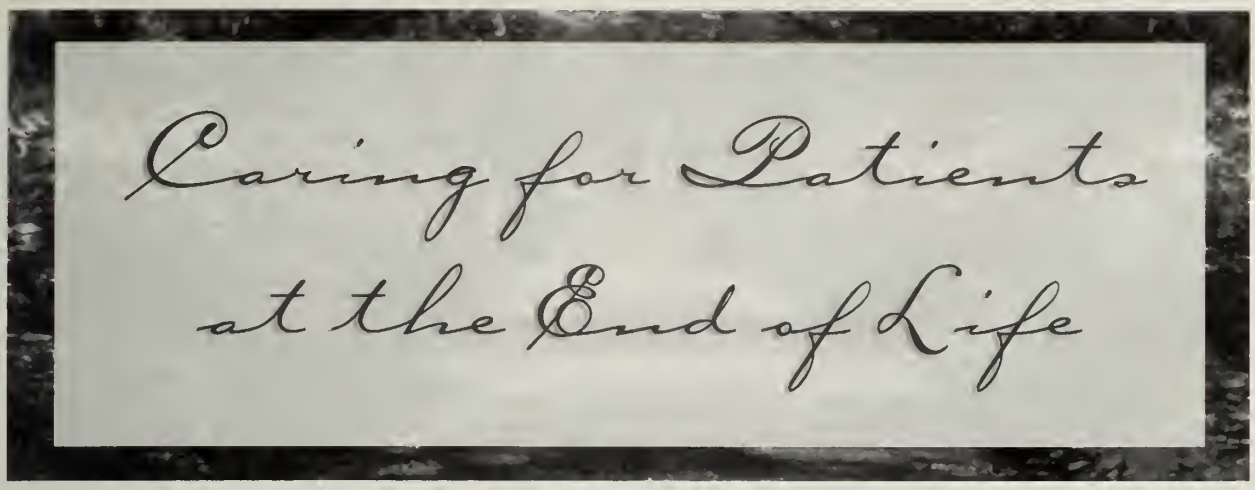
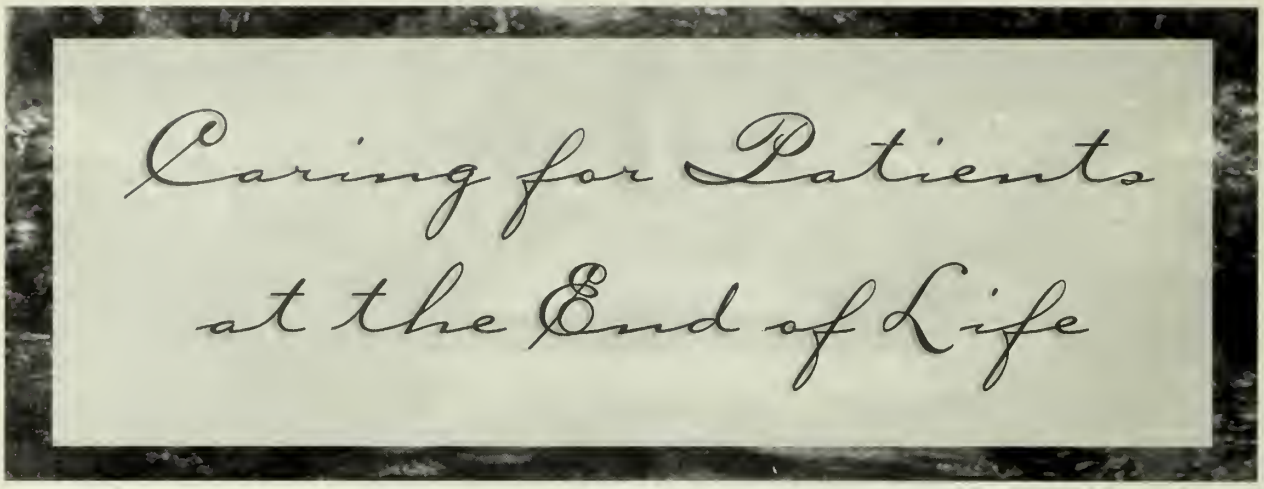


Editor's Comments

This special issue of THE WESTERN JOURNAL OF MEDICINE presents principled and practical information to help physicians and other health care professionals, patients, and families through a passage that we would like to be gentle but that is often stormy. The special editors and authors address end-of-life topics ranging from symptom management to family support, from babies to elders, from prognosis to futility, from ethics to culture to religion, from tempering suffering to balancing economic and clinical demands. Drs Christine Cassel and Gilbert Omenn took meticulous care when selecting authors. Their inspiration and the sum of their intensive work shines in the finished papers. We believe these efforts bring new skills and perspectives, new light and hope.

LINDA HAWES CLEVER, MD
Editor



Dimensions of Care of the Dying Patient

Rising awareness of the need to reckon with the limits of medical care and to provide competent and compassionate palliative care to dying patients has stimulated our bringing together this special issue of THE WESTERN JOURNAL OF MEDICINE. Although the hospice movement, which began in the United States more than 25 years ago, has made great progress in providing appropriate and compassionate care for patients facing the end of life, about 80% of patients still die in hospitals and nursing homes rather than at home or in hospices. The aging of America, widespread use of costly life-sustaining, life-prolonging technologies, and media interest have generated a resurgence of concern about death and dying.

In part demonstrated by the public debate about assisted suicide and euthanasia, many patients, families, and health professionals are seeking a more personal approach to the experience and meaning of death. There is a widespread desire for a dignified and gentle death. Our authors address—from many professional, social, and ethical perspectives—both barriers to and opportunities for a "gentle death."

Physicians are paying closer attention to end-of-life care. Nuland's book *How We Die*[1] and Moore's chapter on "Ethics at Both Ends of Life"[2] reflect the interest among our colleagues. The Institute of Medicine hosted a study group to examine issues about improving quality of care at the end of life. The American Board of Internal Medicine is developing guidelines for residency program directors about clinical competence in the care of dying patients. Foundations have begun to support research to improve the care of dying patients and to develop academic leaders in this area. In Canada, a new specialty of palliative medicine is emerging. The focus on patient satisfaction in the market-centered transformation of health care in the United States further fuels interest.

Overall, birth and death are such profound and fundamental human experiences that patient values and the personal dimension of care should be seen as essential to any measure of quality of care. What are the components of palliative medicine that physicians need in clinical practice? Many aspects are addressed in this special issue.

The first four articles address major dimensions of our culture, often neglected in the press of busy practice, let alone the technologic maze of intensive care units. Callahan describes the broader context from a philosophical and policy vantage point. Medical advances have transformed the context of dying, challenging patients and families to understand their feelings and preferences. Religious views are strong influences for many and may diverge among individuals within a family. O'Connell provides guidance about religious values and constructs. McCormick and Koenig try to help us appreciate these variations in patients' and relatives' values and desires, and to be better able to help them articulate their preferences.

The assessment of a patient's status and prognosis remains the special expertise of physicians. Lynn and colleagues treat this challenging subject. Statistical descriptions of prognosis, based on various measurable elements, will always include notable outliers—patients who die more rapidly, survive longer, or even recover. Some physicians themselves are unrealistically optimistic, perhaps unable to tolerate their own limitations in the face of nature's course. Others find it difficult to admit the failures or limitations of medical treatments, especially with children. Martinson treats special needs of dying children, and La Puma and co-workers advocate the development and utilization of clinical ethics consultants. Such consultants might help resolve conflicts among the several physicians caring for the same patients, as well as identify needs and preferences of the patients and families. They may introduce yet additional views and conflicts.

Gavrin and Chapman remind us that physicians can accomplish much with effective and appropriate management of symptoms that are distressing to patients, to families, and even to the physicians and nurses and other professional caregivers. Pain, nausea, vomiting, dyspnea, anxiety, confusion, and anorexia receive special

attention. MacDonald provides an additional perspective from the research arena on emerging capabilities to managed end-of-life symptoms. As we recognize the futility of many end-of-life diagnostic and therapeutic interventions, discussed by Jecker, we should emphasize the power of medicine to make the final hours, weeks, or months of a patient's life more tolerable, more comfortable, and more dignified.

Bascom and Tolle, as well as other authors in this special issue, emphasize that families require attention during the dying of their loved ones and following the death, as well. Bereavement is not well supported in this society and can be complicated and require medical intervention. The prevention of complications in the bereavement period is good practice.

All of these dimensions of care of patients at the end of life require attention in our training programs and in our continuing education and recertification activities. Blank describes strategies for evaluating clinical competency in these sensitive and, for many physicians, new areas of explicit responsibility.

Finally, managed care has emerged as a potentially dominant form of medical practice and medical organization, not through public policy, but through so-called market forces.[3] Miles addresses the complex economic and organizational influences on physician decision-making at the end of patients' lives. Under prepaid premium arrangements, there is no longer any economic payoff from futile or minimally indicated diagnostic and therapeutic interventions. On the other hand, it is essential to satisfy patients and families that special needs are met, that the managed care organization is not trying to make money by doing less than good medical judgment requires. And investment should be made in services and staff that can support the needs of dying patients.

We want to comment on two other matters mentioned in our introduction. The principles developed by the hospice movement have helped to define desirable management of dying patients. The ideal of hospice care is that a patient should die at home with as little medical paraphernalia as possible, among caring family and in familiar surroundings. Unfortunately, hospice care has been focused primarily on patients dying of disseminated cancer and more recently of the acquired immunodeficiency syndrome and its complications. These conditions have a relatively predictable terminal course and a lot of emotional turmoil for the patients and their families. But they are far from the only causes of predictable death from chronic disease—congestive heart failure, emphysema, liver failure, degenerative neurologic diseases, and Alzheimer's disease are prominent examples, with many elements of manageable suffering. These conditions warrant consideration of hospice-type care, too. Of course, we recognize that many situations are not suitable for hospice, especially when family members or other personal caregivers are not available or not able to provide the care needed, when a safe home setting is not available, or when the trajectory of the final illness does not allow for such planning.

It is impossible to treat the subject of dying patients without considering the requests of an increasing number of patients for physician assistance in terminating a protracted end-of-life condition. The notoriety of Michigan's Dr Kevorkian and the legal tussles there have stimulated public opinion surveys that generally demonstrate widespread support for the option of physician-assisted suicide. Clearly, a great many Americans are overcoming the traditional reluctance to think about or talk about dying.[4] Physicians and ethicists are engaged in lively debate on this deadly serious subject, with concern that criteria for such actions are hard to define and that abuses could threaten vulnerable patients and even the integrity of the medical profession. On the West Coast, less theatrical approaches are progressing. Oregon enacted a proposition legalizing a limited form of physician-assisted suicide, which is currently being tested in court. In the state of Washington, more than 240,000 registered voters signed initiative petitions for a ballot issue in 1992 clarifying the Washington law and permitting physician-assisted suicide. After a campaign that projected horrific behavior by some physicians, Washington voters narrowly rejected that initiative. Subsequently, Compassion in Dying, a nonprofit organization providing support and counseling to terminally ill patients, challenged the law in court. The law was first ruled unconstitutional. A panel then upheld the law two to one on appeal. The 9th Circuit, in mid-1995, set up an extraordinary panel of 11 judges to reconsider that decision. The ruling may be a landmark.

We physicians need to come to terms with our own fears about death and the spiritual context within which we derive meaning from caring for patients at this most profound moment. It can be helpful to draw on cultural expressions in art and literature in discussing these issues with one another and with family and colleagues. Kathryn Hunter, MD, associate editor for this issue, has assembled a sample of such works to illustrate how literature and art can expand and deepen our understanding of the challenges we face in confronting death and caring for patients when they make that passage.

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Frustrated Mastery
The Cultural Context of Death in America

DANIEL CALLAHAN, PhD, *Briarcliff Manor, New York*

The care of dying patients as a problem in the United States cannot be well understood apart from understanding the way in which American culture has responded to the problem of death. This country seems unusual among developed countries in its passion to conquer death, often acting as if death were simply one more disease to be overcome. American medicine has been influenced by this background culture, while adding some idiosyncratic features of its own. A powerful attraction to technology, a fear of malpractice litigation, and a fundamental ambivalence about the response physicians should have to death help to explain why the care of dying patients has been so difficult, so controversial, and so troubling to both the medical and the lay communities.

(Callahan D: Frustrated mastery—The cultural context of death in America, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:226-230)

Writing about death in the United States some years ago, the late historian Arnold Toynbee wryly observed that "death is un-American, an affront to every citizen's inalienable right to life, liberty, and the pursuit of happiness."[1(p366)] Toynbee has hardly been alone in his judgment that Americans seem to have a peculiar attitude toward death. Foreign medical visitors to our country have long spoken with amusement of the apparent belief of many Americans that death is just one more disease to be conquered, a tenacious but not invincible foe. Not too long before his own death, as if to confirm such observations, our late and great physician essayist Lewis Thomas could speak confidently about the imminent and final conquest of all disease. The British writers Jessica Mitford and Evelyn Waugh had a great deal of fun in the 1960s taking apart the American funeral industry, with its devotion to prettifying the dead body for public display. During a recent visit to a Central European country, I was stunned by the medical insouciance toward dying. The general attitude was, "People die—they always have and always will. Why do you Americans make such an issue of it?"

The issue, of course, was people like me, a naive American who had come to think that every country must now have a great struggle over the clinical, legal, and moral problems of caring for the dying. Not necessarily and, in many places, not at all. Why is it that we have had such paroxysms about this, and why has it gone on for so long, at least since the middle of the 1960s? What is there about our American culture that makes our response to death and dying seem so strange to others, and how has that culture affected the medical response to human mortality? It is not the other countries that need explanation. It is ours. In this essay, I want to say something about the history of the question of death in America, the cultural patterns that have developed over the years, and the way in which those patterns work together with medical practices and values to produce many of the problems we now have in the care of the dying.

From the Sacred to the Secular

For the early American Puritans in the 17th century, death was a religious and family event. Funerals were simple and austere, private, and unaccompanied by church ritual, and the deaths they marked were taken as the act of a stern and demanding God. Excessive mourning, considered a judgment on God, was discouraged, and the predominant symbol on tombstones was that of the skull and crossbones.[2] The history of death in America from that time forward can be characterized as a movement from the sacred to the secular, from the private to the institutional, and from the natural to the artifactual.[3]

In the 18th century, the body was given a new dignity. Funerals were held in churches and not just at the grave, as with the Puritans; the virtues of the deceased were eulogized; and the face of a winged cherub replaced that of the skull and crossbones. Puritan austerity gradually gave way to a lushness of mourning and religious ritual. But that phase soon passed, and by the early 19th century, a gradual secularization of death could be observed, with a heavy emphasis on bereavement, a blurring of the line between the living and the dead, more lavish funerals, and a focus on nature, not God, as the cause of death. It is disease that brings about death, not original sin.[4(p26)]

As the 20th century advanced, death was moved from the home to institutions, either hospitals or nursing

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homes. Taken from the hands of family members, it was put under the care of professionals. The emergent funeral industry worked hand in hand with that trend, serving to relieve the family of the practical and emotional burdens of death and to put a greater distance between the living and the dead. By the end of the 20th century, the distance has been even further increased by the rising prevalence of the memorial service, the dead body already gone by the time people gather to remember the deceased. What a British author in 1899 called the "dying of death"—"the practical disappearance of the thought of death as an influence on practical life"—continues apace a century later.[5] "Death," he also wrote, "is regarded no longer as a king of terror, but rather as a kindly nurse who puts us to bed when our day's work is done. The fear of death is being replaced by the joy of life."[5(p4)] If this rosy picture seems to clash with a common view that people are now terrorized by the possibility of an extended, undignified dying, consider a relatively recent Gallup Poll. It found that most Americans claim they almost never think of death or think of it only occasionally.[6]

Although we may well doubt that Americans are as indifferent to death as they say they are, the perennial research optimism about the pending conquest of lethal disease may have something to do with these attitudes. The seeming conquest of infectious disease by the 1960s helped to fuel the war on other fatal diseases that became a hallmark of the medical research enterprise. A number of thinkers in the late 19th century had come to see death as an idealized natural event and looked forward to a painless death in the near future.[7(pp106-107)] But by the late 20th century, the language of a "natural death" came to seem quaint. Nature, many seem to think, is not kindly and requires strong medical intervention to improve the process of dying. The practice of medicine, moreover, has come to treat death as a kind of accident, a contingent event that greater prevention, improved technology, and further research could do away with. Who says people have to die of heart disease, or cancer, or Alzheimer's disease? Only congenital pessimists.

The latest stage of the American story of death might be termed that of the "managed death," a phrase that began appearing in the popular press only in the past decade, but that had deeper roots in western culture. The German philosopher Friedrich Nietzsche at the end of the 19th century voiced an aspiration that now has a highly contemporary ring to it[8(pp536-537)]:

> To die proudly when it is no longer possible to live proudly. Death freely chosen, death at the right time, brightly and cheerfully accomplished amid children and witnesses. . . . From love of life, one should desire a different death: free, conscious, without accident, without ambush.

But it was not in Germany that this idea was most enthusiastically taken up. It was the United States (together with The Netherlands) that embraced this, and then only much later. We tend in this country to think that just about all of life's problems can be reduced to the management level, and we have long put self-determination and freedom at the top of our list of moral and political values.

The idea of a managed death, catching perfectly the American spirit, has taken two forms. In its most benign manifestation, it has taken the form of a desire to terminate treatment at just that moment when further treatment will be futile and when a quiet death is still possible.* In its more radical, controversial manifestation, it has provided the rationale for the euthanasia and physician-assisted suicide movement, which aims to put death under the full control of patients. The late theologian Joseph Fletcher, in his 1956 book *Medicine and Morals*, was wholly American when he argued, a few decades ahead of his time, that medicine has a dual possibility, both of them transcending the traditional cure of illness: that of allowing us to dominate and manipulate human nature, and that of giving us new choices about the living of our lives.[9] For him, euthanasia was the ultimate choice that every person should have, the final triumph of the human will over death.

Now—since the writings of Timothy Quill and other supporters of physician-assisted suicide—the freely chosen, managed death is romanticized: a death that is fully under the patient's control, beautifully orchestrated to allow a final flourishing of familial love and reconciliatory leave-taking.[10] Ironically, death is thus brought back into the home and into the family, where it once was, but now under the aegis of secular self-determination, not under the eye of the fierce and judging God of the Puritans. Nature does not yet provide us with an acceptable "natural" death. It does not measure up to the highest standards of accommodation to our proclaimed right of self-determination or our penchant for dominating control. Thus, it must be tidied up, and how better to manage that than through physician-assisted suicide? I do not count myself among the enthusiasts of that way of coping with the failures of nature to do our bidding, but it is a social force of gathering strength.

Death and American Medicine

American medicine has never been as free of the cultural influences of society as seems to be the case in many other countries. To be sure, American medicine as an institution has had its own independent internal life, full of customs, values, and practices bequeathed it from the Hippocratic tradition. But from the days of Benjamin Rush, it has also shown itself unusually open and susceptible to the broader values (and fads) of American culture. The long and fierce physician defense of fee-for-service medicine that kept America from a system of universal health care at a time when every European country was adopting one mirrored a society that has long had a special love of the market as an economic institution. The acceptance of patient rights and a repudiation of the grossest forms of paternalism mirrored a society that readily and pervasively talks the language of individual rights. The belief that, if there are tragic dilemmas in the provision of health care, they are few and far between, and that the real answer to our present crisis lies in greater efficiency and

*See also N. Jecker, PhD, "Medical Futility and Care of Dying Patients," on pages 287-291 of this issue.

improved quality of services, mirrors a society that often looks to business practices for guidance on the deepest of human matters.

American medicine, embedded in this culture, has approached death with a peculiar, highly idiosyncratic set of values and presuppositions. It seems to blend together the influences of the surrounding society and the peculiar internal traits that set it apart from the medicine practiced in most other countries. The first sign of trouble for this combination was the movement, beginning in the late 1960s, to make institutional death a more tolerable, humane event, a response to the institutional dying that developed after World War II. With exceptional fervor, American medicine had seized on the technologic advances of the 1950s and 1960s to save and extend the lives of patients. Hospitals in particular became the arena for the battle against death: respiratory intensive care units and a steadily expanding array of diagnostic devices were the weapons of choice in this battle. Before long, however, complaints began to be expressed about technologic obsessiveness, an unwillingness to let nature take its course, and the impersonality, even unwitting cruelty, of death in a technologic cocoon. High on the list of complaints was the disappearance of physicians from the bedside of the dying, as if their work was done once a patient was on a downward course, the final stage of life to be left in the hands of nurses. The suspicion was quick to arise that physicians were, if anything, more fearful of death than laypeople.

Three Reforms

The responses to this situation were relatively quick in coming. The advance directive movement, beginning with "living will" legislation in the early 1970s, was one response, aiming to give patients more control over their dying, and particularly the right and the power to have treatment terminated. The hospice movement was another. Imported from Great Britain, it got its start in this country around the same time, aiming to create a different institutional milieu for the care of dying patients and to develop a cadre of people especially trained to provide good palliative care and empathic counseling to the dying and their families. The initiation of courses or segments of courses in medical schools on improved doctor-patient communication and on the moral and clinical problems of terminal care was still another response. Taken together, these three initiatives promised, by the late 1970s, to take care of the challenges posed by dying patients.

Yet, as we look back on the high hopes invested in those reforms, a restrained judgment on their success seems in order. They have all made a contribution to solving the problems, but the problems nonetheless persist. In addition to their inability to sign up any more than 15% of the American public, a body of evidence is beginning to accumulate that advance directives make little difference either in the way patients are treated at the end of their lives or (as some had hoped) in reducing the cost of care in the process.[11] The hospice movement, covered by Medicare in the mid-1980s, has gradually grown, probably encompassing 20% of deaths in this country. But it has had considerable trouble extending its philosophy and methods beyond the care of cancer patients, although vigorous efforts to do so are now underway. The educational reforms have introduced some new topics into the medical school curriculum, primarily in the didactic courses, but they have not become equally prominent in the clinical phase of physician training.

Meanwhile, as those reforms have produced less than the hoped-for changes, a steady stream of court cases, now stretching back to the Karen Ann Quinlan case in 1976, shows no sign of abating.[12] Time and again, families are still forced to go to court to have treatment on a dying relative stopped in the face of medical opposition. A more recent twist, however, has been the opposition of medical staffs to what they judge to be unreasonable patient or family demands for futile or exceedingly marginal benefits. The "futility" debate, initially focused on treatment judged useless or undesirable by patients, has now expanded to include treatment judged useless or inappropriate by physicians.[13] Yet, only in America are these extended and elaborate debates, full of moral heat and philosophical and legal nuance, taking place in any striking way.

I am reminded here of a comment made to me by a visiting Swedish physician at the time of the Quinlan case. That kind of a case could not have arisen in his country, he said, for four reasons. First, there would have been no thought whatever that families should have the right to make decisions about stopping treatment, as the Quinlans were demanding. Second, the issue would never have been taken to court because the courts are not used to solving moral problems in medicine; that is the exclusive domain of physicians. Third, the media would never have heard of the case because such matters were dealt with behind closed doors. Fourth, as a clincher, in his country people tended to agree on most things, and there would not have been a dispute anyway about appropriate treatment. Although that story is some 20 years old now, time and again I hear the equivalent in European countries, those same countries that wonder what all the fuss is about here.

If the various reform movements to improve dying in America have not lived up to the high expectations invested in them, they remain a kind of talisman for many Americans, full of faith that there is an educational, legal, or institutional fix for our problems if only we would apply them. This might only be a matter for the kind of amusement expressed by foreign observers did it not, I suspect, hide a more pervasive unwillingness on the part of many Americans to look death in the face, as if death can be made just one more choice-and-efficiency issue, to be domesticated along with traffic jams and other excesses of modern life.

Reticence About Death

The meaning of death in human life, the appropriate human response to death, and the place of ritual and communal bonds in the face of death are not easy topics for Americans to talk about. Our pluralism and individual-

ism, rightly or wrongly (and maybe a little of both), get in the way. Those matters are relegated to the privacy of religious beliefs (though the churches actually seem rarely to speak of them) or, in their absence, whatever personal resources people can bring to them on their own. There is no sustaining or supportive general culture for grappling with the human reality and importance of death. It is a kind of unspeakable problem, often covered over with much discussion of "death with dignity," which has come to focus on the control, not the meaning, of death.

American medicine's response to these elements in the culture—particularly its tendency to run from death—is further compounded by a number of features of our health care system that enormously bias the system in favor of aggressive treatment of the critically ill and dying. Whereas clinicians have always been forced to accept death, however slowly and reluctantly, no such acquiescence exists among researchers. The National Institutes of Health carries out an unrelenting struggle against death, and for decades, the research budgets and priorities have given the primary place to those diseases that can cause death: cancer, heart disease and stroke, diabetes mellitus, and most recently, the acquired immunodeficiency syndrome (AIDS). Diseases that reduce or destroy the quality of life—deafness, blindness, the dementias, arthritis, osteoporosis, schizophrenia, and depression, for instance—receive considerably less research support.

This situation creates a kind of fundamental rending of the psyche of the medical community: a fresh struggle to find ways for clinicians to better come to terms with death constantly battles a research emphasis that acts as if those diseases that cause death are all capable of being eradicated—in effect, that death itself is a kind of accident, perhaps itself a disease that can be done away with by eliminating its biologic causes. It would sound silly for anyone to say something like that openly, but that is the logic of the research enterprise. But that logic, where death remains a constant enemy, is at war with the new clinical logic that would see death as a part of life, to be accepted gracefully at some point.

Inevitably, that research attitude spills over into clinical practice, where it is commonly thought—if not rationally defended—that many deaths, perhaps most, could be averted if only there were better preventive medicine, better individual health behavior, better screening, better care, or—all else failing—better and more research. Is death a friend or an enemy, to be acquiesced to or to be fought? American medicine is simply not sure about the answer to that question. Two major textbooks of medicine, Cecil's and Harrison's, perfectly reflect this ambivalence.[14,15] Though filled with descriptions of, and treatment strategies for, the full panoply of fatal diseases, the word death itself is scanted, the care of the dying sequestered to special sections, and the emphasis placed almost wholly on restoring health, not the routine medical care of the dying. Both books seem to have overlooked the fact that everyone eventually dies, and of some disease dealt with in those textbooks.

The fundamental schism at the heart of American medicine is compounded by a number of troublesome features of the health care system. It is a system filled with incentives for aggressive treatment, pushing the envelope of continued life as far as is possible. The highly technologic and technocratic training of American physicians helps to set the stage, giving a high place to action and technologic persistence. The starting and continuance of treatment are emphasized, not its termination. The attitudes instilled by that kind of training are then reinforced by a malpractice litigation environment that leaves most physicians feeling at risk of a lawsuit should they not provide a "full-court (that is, technologic) press" to their patients. A fear of doing wrong, or of making a mistake, often overshadows a desire to do good and a willingness to take some chances.

Finally, at least until recently, the system of fee-for-service medicine, combined with third-party payment for health care, often provided a powerful economic motive for continued treatment. The bias of third-party payment toward the wielding of specialized, normally technologic skills only exacerbated that tendency. The combination, then, of training, malpractice fears, and financial incentives all push in one direction, toward more treatment, not the abatement of treatment. Whether the powerful surge to managed care, the press for cost control, and the continuing agitation to reduce the cost of terminal care can change this bias remains to be seen.

An Open Wound

I cannot claim that I have found the bottom of the mystery of why American culture and American medicine seem to have a set of attitudes, values, and practices not only at variance with most other countries and cultures, but also of a kind that seems to work so badly and so disjointedly for us. If one could say that, yes, our values and practices are a little odd, but they work nicely for us, thank you, then the whole matter could be put aside. But they do not work well for us. The care of the dying has remained a kind of open moral wound in our health care system, bedeviling us for decades now, full of hopeful initiatives that do not quite work out, court cases that only give way to further cases, and moral solutions that seem to require still further moral solutions to clear up the problems created by the earlier ones.

If the roots of our national problem with the care of the dying lie deeply within the American character, then we have a long and hard struggle before us, not easily amenable to the kind of legal and administrative manipulation we seem to depend on to get us out of our difficulties. As Michael Ignatieff ("Modern Dying," *The New Republic*, December 26, 1988, p 32) has perceptively written:

> Cultures that live by the values of self-realization and self-mastery are not especially good at dying, at submitting to those experiences where freedom ends and biological fate begins. Why should they be? Their strong side is Promethean ambition: the defiance and transcendence of fate, material, and social limit. Their weak side is submitting to the inevitable.

The secularization of death in America, replacing a religious with a medical response, is a major part of our national weakness in submitting to the inevitable. Yet, if that medical response could somehow find a way to get over its reticence about talking about death and no less get over its view of death as somehow the ultimate enemy, it would be in a better position to develop those attitudes and practices necessary to help everyone die as good a death as humanly possible. But American medicine cannot achieve that goal alone. That will require a shift in American culture itself. Is that possible? Yes. The combination of financial pressure, a broad-based concern about how we die in this country, and at least some growing resistance to a technologic solution to death all set the stage for a shift. Only time will show whether it can actually take place.

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Religious Dimensions of Dying and Death

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Death, the hard task-master, spares the rose as little as the thistle; he forgets not a solitary blade of grass in the remotest wilderness; he thoroughly and incessantly destroys. Everywhere he grinds to dust plants and animals, men and their works.

Italian Travel Sketches
HEINRICH HEINE, 1829[1]

The dying process and death, essential features of the human condition, command attention. Most of us struggle with the certain knowledge that we must die, especially when we are actively involved with someone who is gravely ill and dying. We look inquisitively into that person's life, and, recognizing ourselves, we ask why. Life, whatever else it may be, is a journey toward death.

Care for the dying constantly challenges patients, their families, caregivers, and, as the current debate about euthanasia demonstrates, society at large. The environment of death is a powerful stimulant to reflection on the significance of human life and destiny. Everyone who experiences the shudder of the fear of death confronts disquieting questions about life's meaning and death's place. It is within the context of these searching questions that death as an integral part of our human existence resonates most deeply with religious concerns about the meaning of life.

Religion is often invoked as a repository of time-tested wisdom and practical guidance as we deal with our natural fear of finitude. But, as William James taught some time ago, religions come in many shapes and forms. And they inspire a wide variety of contradictory responses: love and hate, adherence and rejection, tolerance and bigotry.

Religion Generally Described

Although religion eludes simple definition, the philosopher-theologian Paul Tillich (1886-1965) developed a classic and, for our purposes, sufficiently comprehensive and accessible description of religion as the most fundamental aspect of the human spirit—the depth dimension of our shared humanity. For the sake of clarity and convenience, I will draw exclusively on Tillich's broad definition of religion that has proved useful to people in many Christian and non-Christian traditions, as well as those who have adopted secular forms of spirituality. Tillich defined religion as "the encounter with the holy, and the holy can be defined as the manifestation of what concerns us ultimately and with unconditional seriousness."[2(p152)]

Tillich's image of depth conveys the sense that

> the religious aspect points to that which is ultimate, infinite, unconditional in [human] spiritual life. *Religion, in the largest and most basic sense of the word, is ultimate concern.* And ultimate concern is manifest in *all creative* functions of the human spirit [emphasis added].[3(pp7-8)]

Unlike other important religious thinkers, Tillich insisted that religion is not a special function or an isolable dimension of the human spirit. It is the depth dimension that permeates the entire range of our human endeavors. For example, religion does not stand alongside the intellectual, moral, and aesthetic functions; it is the dimension of depth in all of them. As we move toward the deepest levels of meaning, whether in art, science, ethics, or in some other expression of the human spirit, we encounter religious space and the echo of ultimacy. Religion as "ultimate concern" plunges us toward the core of our being, where we recognize and acknowledge that which matters to us most. Religion comprises our underlying value orientation and the fundamental convictions that shape our lives, those things that are most meaningful to us.

Tillich provides a concise yet profoundly evocative summary of religion as the depth dimension of human existence[3(p9)]:

> Religion opens up the depth of [human] spiritual life which is usually covered by the dust of our daily life and the noise of our secular work. It gives us the experience of the Holy, of something which is untouchable, awe-inspiring, an ultimate meaning, the source of ultimate courage.

Tillich sees religion as so essentially a part of our humanity that he understands every person to be potentially religious. Because ultimate concern of some kind is a universal human possibility, religious experience, even if it goes unnamed, is part and parcel of everyone's life—just like death.

The experiences associated with dying and death are profoundly religious in the Tillichian sense. As a life is ending, either our own or someone else's, we confront the ultimate meaning of human existence in general, and perhaps more important, we reckon with the meaning of our own individual lives. We look "religiously" into the core of our being in search of those fundamental values

(O'Connell LJ: Religious dimensions of dying and death, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:231-235)

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that can shape the experience of death and guide us across the threshold. The dying process, then, is a religious rite of passage, irrespective of one's adherence to any particular religion or special body of beliefs and practices. The proximity of death, whether it be in the bedroom, the clinical setting, or on the battlefield, makes the ordinary setting sacred. The hush that falls over the space surrounding the newly dead and the ritual of postmortem care give poignant witness to the solemnity and religious overtones of the occasion. Ultimate concern erupts from the depths of our being whenever the proximity of dying and death clears away "the dust of our daily lives," silences "the noise of our secular work," and sends us searching for "the source of ultimate courage."

Tillich's definition of religion as the dimension of depth in all of life's functions was the central organizing concept of his distinctive theory of religion and religious symbolism. Unfortunately, we cannot exploit the full richness of that theory in this article. Tillich's explanation of the religious impulse and its relationship to dying and death, however, provides a suggestive point of departure for explaining the role of religion in caring for patients at the end of life, as well as caring for those who care for them. By describing religion as the "ultimate concern . . . manifest in all creative functions of the human spirit," he at once explains the essence of the religious experience and opens the way for the practical application of his guiding insight.

Religious Traditions

Tillich fixes on "ultimate concern" as the essence of religion and the foundation for all concrete historical religious traditions, which serve as vehicles for understanding and expressing the depth dimension of human life and destiny. Religious traditions strive to give symbolic access and concrete visibility to the deepest levels of human existence, especially at critical turning points like terminal illness and death, when the search for meaning becomes intense. In short, ultimate concern is interpreted and "acted out" in the many theaters of religious tradition. Here ultimate concern is manifested in the flesh and bone of individual existence, emerging as the source of personal meaning, the fount of moral insight, and the guide to purposeful behavior in the face of life's challenges.

Drawing on Tillich's basic insight, we can illustrate the practical effects of ultimate concern by exploring three central creative functions of the human spirit as they shape religious traditions in general and as they inform the response of persons who are involved with the dying process in particular. The intellectual, the moral, and the aesthetic aspects of the human spirit each play a distinctive, yet complementary, role in bringing deeply embedded ultimate concern to the surface of our everyday lives. These creative capacities each mediate the ultimate concern and allow us to relate to it in various ways: Our intellectual powers give it concrete meaning in the here and now so we can "know" it, our moral sense provides guidance so we can "act" on it, and our aesthetic sensibility gives it form so we can "express" it purposefully. Religious traditions draw on these creative gifts of the human spirit to develop distinctive worldviews (theology), moral values (religious ethics), and aesthetic practices (religious ritual and spirituality) that reflect ultimate concern and address existential questions like the meaning of death.

Role of Theology or Religious Doctrine

Within the intellectual realm, the realm of knowledge, a religious tradition articulates its theology or rational commentary on the world. For example, religious traditions usually offer specific interpretations of the origins of the world and human life. Jews, Christians, and Muslims hold that God created the world, whereas Hindus believe life sprang from the Mother of All, that is, the Ganges River, and the Navajo believe our world "takes its beginning in a primordial underground world that is dark and black."[4(p127)]

Moving beyond theories of creation, religious traditions tend to develop a set of core ideas or doctrines that serve as the touchstone of meaning and source of insight regarding human life and destiny as a whole. Important events like birth, marriage, serious illness, and death are framed and interpreted in light of these religious teachings. Issues in health and medicine are also often interpreted religiously. There is an acknowledged kinship between religion and medicine. As religion scholar Raoul Birnbaum explains,[5(p33)]

> [D]isease is a somber mystery, a powerful transformative process that leads to the gateways of death. Both physician and the religious specialist have much concern with this boundary between life and death, and those who are especially effective at their callings traverse with respectful familiarity along this distinctive edge.

Given this congeniality between religion and medicine, most religious traditions offer theologic opinions on the pursuit of good health and the management of health-related problems. For example, Catholicism rejects in vitro fertilization as a remedy for infertile couples, Orthodox Judaism does not accept brain death criteria, the Jehovah's Witnesses reject blood transfusions, and Christian Science shuns mainstream medical treatment. Hinduism would discourage a surgeon from operating "(except for life-threatening emergencies) on a new-moon night, which is considered inauspicious for undertaking any significant activity."[6(p6)]

In line with their general interest in questions of health and medicine, religious traditions attend to death and dying. The significance and management of the dying process is a prominent theme in most theologic systems because, as we have seen, it engenders the existential question of ultimate concern. Religious doctrines on dying and death represent the creative, intellectual response of the human spirit as it strives to understand and rationally explain our puzzling human finitude: What is the meaning of life, of suffering, and of death?

In providing care to dying patients, religious belief systems often play a prominent role. Within the pluralistic context of the United States society, where more than 80% of the population claims to be religious, the religious dimension comes into play in most care settings. Given US culture, knowledge about and respect for religious traditions can only enhance the care of the dying.

Theology or religious belief systems contribute in at least two important ways. First, they provide solace, self-understanding, and emotional stability as deep questions about life's ultimate meaning surface. Patients and caregivers often turn to their religious convictions to fortify themselves and find consolation as death approaches and they confront "this intrusion of the alien into the familiar, the menacing into the reassuring, the irrational into the orderly."[7(p53)] The religious dimension serves as a defense against the insecurities and emotional upheaval associated with impending death. The Christian doctrine of eternal life, for example, provides many people with an assuring, symbolic answer to the existential question of death. It helps them face the inevitable with a sense of hope and relative calm. Caregivers should be aware of such religious sources of affirmation and even consider tapping into them when appropriate.

Second, analysis of the respective religious beliefs of caregiver and patient can expose and explain tension in the relationship. For example, Roman Catholic and Hindu physicians are well advised to develop an appreciation of the theologic framework that shapes the life of some Orthodox Jewish patients. It would be helpful for them to know, for instance, that some Orthodox Jews adhere to interpretations of the Jewish religious law that hold that brain death is not sufficient to establish a person as dead. Some well-known teachers like Rabbi J. David Bleich believe that even brain death and irreversible coma are not sufficient to establish a person as dead in Jewish law.[8] As reported by Ellenson, "Jewish sources on the subject, in Rabbi Bleich's opinion, clearly define death as the complete cessation of cardiac and respiratory activities with no hope of resuscitation."[8(p222)] Other Jewish authorities would invoke the paramount value and sanctity of life to reject another medically and legally sanctioned practice, the withdrawal of artificial nutrition from someone in a persistent vegetative state. Because brain death criteria and the withdrawal of artificial nutrition are not contrary to Catholic teaching or the Hindu religious tradition, well-informed Catholic or Hindu physicians will be less likely to offend the religious sensibilities of Orthodox Jewish patients by unintentionally imposing a Catholic or Hindu worldview on them. Conversely, Orthodox Jewish physicians will need to understand the Catholic and Hindu points of view that shape the experience of many terminally ill patients and their families. The Catholic and Hindu traditions, although utterly committed to life as a basic good, are relatively less tenacious about sustaining it beyond a certain point. Thus, from a theologic perspective, the issues of brain death and the removal of life support systems are relatively less complicated for Catholics and Hindus.

Some familiarity with common religious views, or the ability to gain quick access to such views, will benefit caregivers, patients, and families, especially within the meaning-laden milieu of dying and death.* Awareness of specific religious tenets and how they shape perceptions and practices surrounding death will undoubtedly enhance communication and minimize the potential for conflict at critical turning points in the care of the dying. The pastoral care department often serves as a ready resource for caregivers and families.

Although religious belief has a powerful influence on patients' perceptions, preferences, and choices, the influential role of religion in the personal life and professional practice of many physicians is no less important. As Reynolds and Stone have noted so well, "[I]n the process of caring for patients, physicians have a unique—and privileged—window on the full range of human emotions."[9(p13)] But physicians are more than mere observers; they are participant-observers. Their own emotions and death fears are inextricably bound up with the suffering and death of their patients. Extreme stress and unnerving ambiguity sometimes lead to exhaustion, emotional fragmentation, and the erosion of meaning in their lives. For many physicians, spiritual and explicitly religious convictions provide a deep reservoir of meaning, a stable sense of self, and an abiding sense of vocation. They interpret their intimate involvement in the mysteries of life and death as experiences of "the Holy, of something which is untouchable, awe-inspiring, an ultimate meaning, the source of ultimate courage."[3] They find strength and refreshment in their faith, that is, in their conviction that life—including death—does make sense.

Role of Religious Ethics

Within the moral sphere, the sphere of conduct, religious traditions develop ethical systems about right and wrong actions. For many people, religion provides insight and normative guidance for making decisions. It provides perspective and moral resources for those who struggle with health-related decisions. It is natural that religiously inspired moral attitudes become an integral dimension of the decision-making processes that affect the dying. Religious ethics represent the moral response of the human spirit as it encounters dying and death: How does one act as death approaches? What counts for good? What constitutes evil?

In the age of high-tech medicine, end-of-life decisions are generating more ethically charged discussion

*There is also a steadily growing body of literature in this area. The critically acclaimed "Health/Medicine and the Faith Traditions" series from The Park Ridge Center for the Study of Health, Faith, and Ethics in Chicago, Illinois, explores the ways in which major religions relate to universal issues of health: suffering, madness, sexuality, healing, well-being, dignity, mortality, life passages, care, and dying. Among the series authors are theologians, historians, ethicists, and physicians. Volumes on 14 traditions—Lutheran, Reformed, Catholic, Anglican, Jewish, Methodist, Islamic, Christian Science, Hindu, Eastern Orthodox, Native North American, Latter-day Saints, Evangelical, and Anabaptist—have now been completed (New York, NY, Crossroad Publishing Company, 1986 to 1995).

than ever before. It is no surprise, then, that religious groups have been active in the debates about euthanasia and physician-assisted suicide. Religious groups may be either for or against euthanasia, but there is a clear sense that this issue resonates with their deepest concerns about the ultimate meaning of human life and destiny. The specter of orchestrated death agitates the religious depth dimension of the human spirit, as described by Tillich, and elicits moral reflection within religious traditions. Certainly, religious ethics will become more prominent when and if physician-assisted suicide enters the mainstream. Deep-seated ultimate concern will continue to stir the moral consciousness of individuals and communities as society struggles to achieve some consensus on this troublesome issue.

The issue of medically futile treatment has also been framed in terms of religious ethics. Recently, the case of Baby K, an anencephalic infant, illustrated the effects of the religious dimension on the issue of dying and death. Although physicians had determined that Baby K's condition was incompatible with life and that thus continued treatment would constitute futile medical intervention, the infant's mother insisted that Baby K should be sustained because God might choose to work a miracle. She believed that the will of God, not the medical expertise of physicians, should dictate the right course of action. In her defense, Stephen G. Post insisted that

> religious beliefs should not be trivialized in clinical ethics, even if reason, not belief, is the language of the public forum; . . . free exercise of religion deserves serious discussion in the futility debate, and significant religious accommodation must be included in any hospital or societal futility policies.[10(p20)]

Because the practices of religion and medicine often overlap, the religious ethics of patients, families, significant others, caregivers, and even institutions will undoubtedly affect the development of a treatment plan and, in some cases, the use of specific medical interventions. There are definite points of convergence where medicine and religion are mutually supportive; but there are also areas of divergence and conflict. When the goals of medicine and religion are at odds, physicians can be trapped between their desire to respect the religious convictions and autonomy of their patients, on the one hand, and, on the other hand, their obligation to adhere to the standards of sound medical practice. Sometimes there must be a parting of the ways, because physicians should not be compelled to violate their own moral convictions and professional standards to accommodate the religious beliefs of others. As Paris and Reardon put it,[11(p133)]

> Physicians as moral agents should exercise professional judgment in assessing patient requests. If the request goes beyond well-established medical criteria of reasonableness, the physician ought not feel obliged to provide it.

Refusal to comply with patients' or families' requests for medically pointless procedures based on religious beliefs "is not abandonment of the patient; it is an assertion of professional responsibility."[11(p133)] Before withdrawing, however, the physician should carefully explain his or her objections to the proposed treatment and, if possible, arrange a conference with the ethics consultation service, the ethics committee, or a representative of the pastoral care department. Frequently an acceptable consensus does emerge, thereby averting the tragic rupture of the physician-patient relationship.

Role of Religious Ritual

The death of a patient generates awe and excites feelings of ultimate concern. Responding to the gravity of the situation, nurses tend to approach the newly dead with a sense of propriety and respect as they prepare it for transport, cleansing and wrapping it with almost ceremonial tenderness. These stylized nursing rituals represent the aesthetic function of the human spirit as it brings ultimate concern to explicit expression. The very core of a person's being is touched when she or he encounters a corpse and ultimate concern pushes its way to the surface. Ritual enactment replaces routine practice because, as William May reminds us, "most people express their 'ultimate concerns' chiefly through rituals."[12(p12)] The creation of rites and rituals provides an organized and symbolically meaningful pathway through serious illness to death and beyond.

Religious traditions abound with rituals surrounding the expression of ultimate concern at the time of serious illness and death. The Christian sacrament of the sick and the dying; the Jewish *taharah* or ritual cleansing of the body; the Islamic wailing ritual; the Hindu practice of offering a *pinda*—a ball of rice or flour—to the dead person's spirit; and the stylized lamentation, ritual weeping, shouting, and ceremonial fury that are part of burial practices among indigenous South Americans are all religious expressions of ultimate concern. They enable individuals and communities to purposefully express and enact their response to dying and death. They allow the human spirit to cry out against the ineffable mystery of our mortality and at the same time embrace it with dignity and decorum.

Religious traditions create space and offer structured approaches for individuals and communities to celebrate, remember, and deal with the emotional and social burdens associated with dying and death. Religious ceremonies before death often provide opportunities for both patients and family members to achieve closure and compose themselves as they prepare for the end. Those who care for dying patients, especially patients coming from greatly different cultural and religious backgrounds, can enhance the quality of care by understanding and, when appropriate and feasible, incorporating religious milestones and symbolic events into the care plan.

Conclusion

An informed perspective on the origins and role of religion in the lives of individuals and communities is a definite asset when assisting in the care of the dying. It provides a vocabulary and point of reference for meaning-filled communication. A well-attuned caregiver will find pregnant hints and subtly expressed desires couched in the religious language that often surrounds the dying

process. As "the source of ultimate courage" for many persons, religion often provides final consolation and ultimate direction in the face of death, and it should be recognized and respected for that.

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* * *

Hospital Parking Garage

He is just my father's age
and her nightgown blazes in a paper bag,
an open grief of objects
marked Property of Ida Jennings.

Who will hold him in the bluish glow of morning?
He climbs into an old gray car
and sets the paper bag carefully
on the seat beside him.

He has no talent for making up a life.
Flowered bedsheets surprise him.
Tonight he will have much to hear,
years ticking in every creak and sound.

His hands lie idle in his lap, then he turns
the key. Everywhere the world is disappearing.

JEANNE LEVASSEUR

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Caring for Patients at the End of Life

Patients' Perspectives on Dying and on the Care of Dying Patients

THOMAS R. McCORMICK, DMin, *and* BECKY J. CONLEY, MD, *Seattle, Washington*

Dying patients have much to teach us about their preferences for care. Although caring for dying patients is a major responsibility of physicians, the current curriculum in medical education emphasizes the pathophysiology and treatment of disease, with scarce time and emphasis for developing attitudes and skills essential to caring for persons in the final stage of life. Barriers to satisfactory communication may arise from either the physician or the patient, or both. Patients and physicians sometimes attach different meanings to words that are commonly used in discussing treatment. Barriers can be diminished or resolved by applying good communication skills, including attending to both verbal and nonverbal signals, exploring incongruent affect, and empathically eliciting patients' perspectives about illness, treatment plans, and end-of-life issues. The competent care of dying patients must extend beyond the management of physical symptoms because patients may experience their gravest suffering from fears and anxieties that go unaddressed in conversations with their physician. Conflicts arise when the disease progresses and the end of life approaches if the physician and patient have not reached agreement on their expectations. Physicians may initiate life-prolonging mechanisms when patients actually prefer palliative care.

Patients experience a reduction in both physical and psychological aspects of suffering when physicians use good communication skills, are sensitive to patients' perspectives, and actively work to reduce barriers to mutual understanding.

(McCormick TR, Conley BJ: Patients' perspectives on dying and on the care of dying patients, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:236-243)

Despite the medical profession's ambitious goals of healing the injured and curing the ill, death is a natural and inevitable end of human life. All will die. Therefore, another important goal of medicine is caring for the dying. Fortunately, some physicians perceive it a special privilege to be able to participate with patients in the last stage of life's journey. These physicians are perceived by patients and families as competent, warm, and caring communicators who are willing to be involved at a personal level in the provision of care.

Many physicians feel uncomfortable when a patient is dying and nothing of a curative or technical nature can be offered. Feelings of discomfort may lead physicians into a variety of unplanned behaviors that create a safe emotional distance from their patients. When dying patients experience their physician as distant or uncomfortable, they feel depersonalized and inhibited in openly discussing their most important concerns in the final phase of life. Patients' questions can be an opportunity to provide information that could reassure them about comfort measures that would be implemented as their condition worsens and how their dying could occur with appropriate support.

Patients are also sensitive to the nonverbal language of their physician. For example, an alert, competent 66-year-old man with bladder cancer tried to elicit information about the progression of his disease from two different physicians assigned to his care. In response to the question, "How is my disease responding to treatment?" the first oncology fellow lowered his eyes to the chart, flipped through the pages, and mumbled an answer so loaded with medical jargon that the patient could not understand the physician's response. He correctly concluded from this behavior that the physician was reluctant to discuss his condition. When the patient posed the same question to the second fellow, she offered reassur-

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The University of Washington is one of ten medical schools engaged in a study designed to evaluate and improve methods of teaching medical students the art of caring for dying patients and their families. Dr McCormick, who teaches death education for University of Washington School of Medicine students, serves on the National Advisory Panel for Choice in Dying, sponsored by a grant from the Greenwall Foundation.

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ance as tears welled up in her eyes. The patient later told his wife that he believed her tears more than her words.

Patients are usually most satisfied when they can get information about their condition and care directly from their physician. When the patient in the previous paragraph finally learned from his adult daughter that his prognosis was grim and he was expected to die in the near future from his rapidly progressing tumor, he was further chagrined that the information had been shared with his daughter before it was disclosed to him. Effective communication plays an important role in patient satisfaction and response to treatment and can actually reduce patients' suffering by recognizing their personal needs, feelings, and expectations.[1]

Dying is a normal part of living. No single way of dying is ideal, yet there are some general principles that can guide us in providing care for the dying. Persons tend to die in character, so an important goal in working with dying patients is to allow or assist a person in the integration of dying into his or her lifestyle. Weisman describes this as an "appropriate death," living out our dying in a manner consonant with our values and coping mechanisms.[2] Dying is person-specific, and the "final agenda" of every person will be unique when it comes to reconciling death with life and appropriately maintaining relationships as death approaches. For example, Cassell describes a 35-year-old patient who had received extensive treatment for widespread metastatic breast cancer. Cassell observed three facts about her situation[3(p31)]:

> The first is that this woman's suffering was not confined to physical symptoms. The second is that she suffered not only from her disease but also from its treatment (it was disfiguring). The third fact is that one could not anticipate what she would describe as a source of suffering; like other patients, she had to be asked.

In an elective class on death and dying, we ask medical students to write two paragraphs, the first describing their concept of a bad death and the second describing their concept of a good death, the kind of death they would want for themselves. These descriptions are shared with the class, and it is common for one person's "good death" (for example, sudden, unexpected death from massive heart attack) to be another's perception of a "bad death" and vice versa. This exercise helps reinforce the principle that we avoid projecting our values onto patients, but that we put forth the effort to understand patients' perspectives.

Patients' Perspectives

Although the literature is replete with research into the attitudes and practices of physicians in caring for dying patients, until recent years, little research has been directed specifically toward patients' perspectives on communication during a life-threatening illness and patients' perceptions of support from the physician-patient relationship.[4] In the not-too-distant past, physicians typically withheld the fact that a patient was expected to die. As recently as the 1960s, most physicians in the United States (90%) did not directly inform patients of the diagnosis of a life-threatening illness, particularly cancer.[5]

Furthermore, the person in the "sick role" in this era, as described by Parsons, was viewed as a passive participant who was expected to cooperate with the physician-expert and comply with the physician's advice.[6] A pioneer in patient communication, Kübler-Ross broke the taboo of speaking directly with dying patients about their feelings.[7] She reported that most patients found relief in being able to talk openly about the process of dying. In current practice, the emergence of new therapies and the requisite demand for informed consent has further reversed this practice. Most patients are now informed of the nature of their diagnosis, their prognosis, and the preferred course of medical treatment.[8]

Despite these advances, much work is still needed in improving the communication between physicians and patients surrounding end-of-life issues. A recent study of 228 adults found that 40% of the terms used by physicians were not understood by their patients.[9] Many physicians withhold information, fearing that full disclosure of an incurable illness will rob the patient of all hope for the future. Textbooks like *Harrison's Principles of Internal Medicine* still advise that physicians should decide how much information to convey based on factors such as the financial and business status of the patient, the religious beliefs of the patient, and the wishes of other family members.[10(p5)] These factors might militate against providing information that patients desire to know. Waitzkin's research indicates that patients wanted to know as much information about their situation as possible and thought it was helpful, whereas physicians underestimated their patients' desire for information in 65% of study cases, overestimated in 6%, and estimated correctly in 29%.[4] The principle of

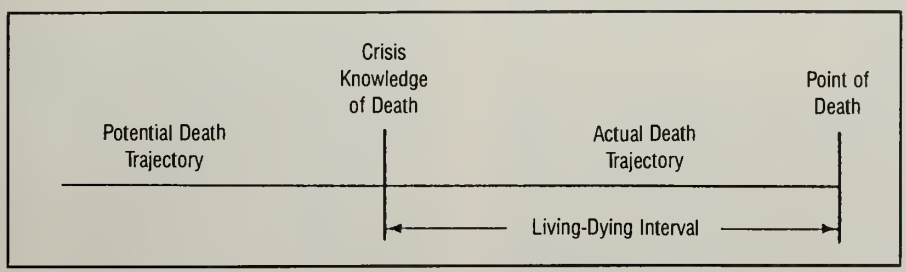

Figure 1.—Living with the awareness that life will be foreshortened precipitates a crisis.

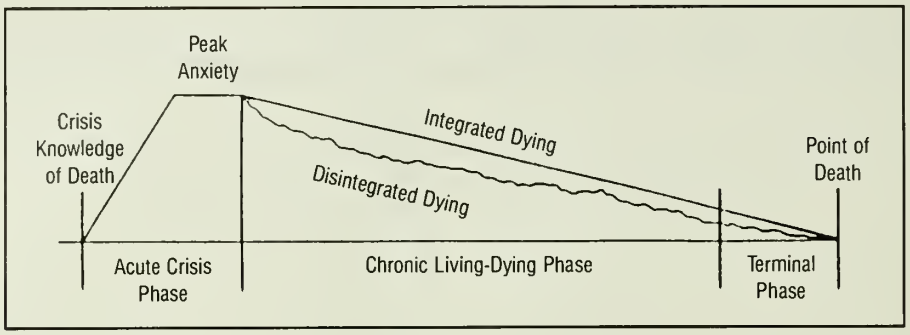

Figure 2.—With appropriate support, patients can use the awareness of their dying to integrate their values by responding to relationships and revising goals in the time that is left to them. Without such support, patients may experience a disintegration at the psychological and social levels in the chronic living-dying phase before death.

open communication should allow patients to have their questions answered in a compassionate and unhurried manner, with assurance by their caregivers that their emotional, physical, and spiritual needs will be provided for or arranged.

Living With Denial

Human beings live with an awareness of mortality and the potential for death at any time, although we ordinarily project a picture of ourselves as alive in the foreseeable future. Becker describes the mechanism of normal denial that removes the idea of death from our everyday deliberations and conveniently stores it just out of sight or consciousness.[11] Thus, the discovery that our future life span will be foreshortened by illness or accident precipitates a crisis—the crisis of the knowledge of death.[12(p44)] When our potential life span is shortened by the threat of illness, all anticipated activities must be recast within a changed time frame.

To teach empathy with patients in a class on death and dying designed for medical students, we ask students to write down their current age, then the age at which they expect they will die, and then to list their important priorities in the time that is left. Later in the same session, we invite them to imagine that they have just learned they have six months to live and, in the light of this shortened time frame, to make any desired adjustments to their priority list. In most cases, the priority lists change dramatically, and most students claim they would withdraw from medical school, spend more time with their families, travel, and seek pleasures deferred for medical studies.

Crisis of Disclosure

When a physician discloses the diagnosis of a life-threatening illness, the door of awareness is jarred open for a patient. The usual habit of allowing thoughts of death to remain in the background is now impossible. Death can no longer be denied. This awareness precipitates a crisis for most patients, who are suddenly faced with addressing, and most likely rearranging, their priorities in the time they now anticipate is left.

Pattison offers two diagrams that illustrate the emotional work that is precipitated for most patients in the living-dying interval between the crisis knowledge of death and the point of actual death (Figures 1 and 2).[12]

In this perceptual model, the awareness that death is near leads to an acute crisis phase, followed by a chronic living-dying phase, and, finally, the terminal phase leading to the point of death (Figure 3). Health care professionals have much to offer in helping patients to cope during each of these phases. Kübler-Ross observed that patients in a hospital often experienced feelings of shock, numbness, denial, and anger in this acute crisis phase after learning they will die.[7] In a personal conversation with one of us (T.M., February 12, 1985), Kübler-Ross expressed regret that she had referred to these as "stages" of dying, as some came to believe that patients should progress through these stages in a step-like manner. Rather, she had intended to describe patterns of emotional response that she had observed in many patients to help others recognize the naturalness of these feelings and to provide emotional support for patients experiencing these feelings.

Likewise, in the chronic living-dying phase, patients may need help and support in integrating their dying into the activities and circumstances of daily living and adapting to the limitations brought about by the illness and its symptoms. Kübler-Ross observed that some patients enter into a bargaining process, often experience depression, and may move toward the acceptance of their death as they integrate the inevitability of death in this period.[7,12]

When patients learn that no curative treatment is available for their illness, they often have a number of fears and anxieties. These may arise in any of the three phases described earlier, following the knowledge that death is inevitable. Patients may fear the onset of pain that cannot be managed, the loss of bodily control, the loss of function, and a growing dependence on others. Patients may also fear the unknown, the loss of family and friends, and, ultimately, the loss of self.[12] Health care professionals have a moral duty to provide adequate pain management and symptom control. Fear of inade-

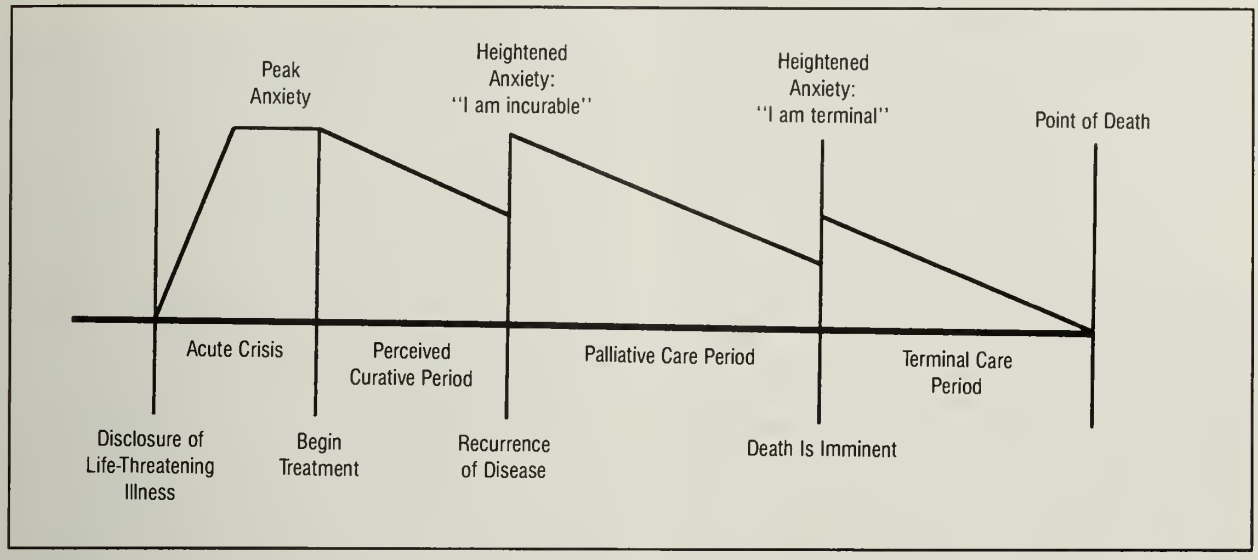

Figure 3.—This diagram from the patients' perspective shows heightened anxiety at the time of diagnosis, when the disease recurs, and when it appears death is imminent. Communication and psychological and social support are especially important at these times.

quate pain management has contributed substantially to the recent interest in physician-assisted suicide. Fortunately, there is a growing movement in pain management that is actively teaching and carrying out comfort measures appropriate to the needs of patients.* We need to go beyond pain management to address the suffering of patients, however. Only a portion of suffering is attributable to physical pain; other aspects are psychological and emotional and can be ameliorated and assuaged by caregivers who remain responsive to the patient as a person.

A Small Qualitative Study

To better understand the needs of dying patients from their own perspective, we interviewed six patients with life-threatening illness. Having noted patients referring to a "transition" from curative measures to palliative measures, we were interested to learn more about how physicians can help patients recognize this transition and provide support in this process. As described previously, patients have notable levels of awareness in their perceptions of their illness and its treatment and the meaning that they attach to these changes. Physicians, possessing a greater body of knowledge of the nature of disease and its treatment, often form their own perceptions and assumptions about the likely future course of any particular patient. The disparity of information and beliefs held by physicians and patients often leads to problems in communication.[13] It is important that physicians take time to listen to their patients' stories and to ask about their thoughts, feelings, and concerns throughout the changing circumstances of treatment and care.

Here we describe the cases of six patients who, having accepted hospice assignment, were clearly aware that their illnesses were no longer responsive to curative measures and that death was fairly imminent. Patients who are aware of their impending death are able to share something that others cannot—their experience of dying. These patients were willing to share experiences from all aspects of their care over the course of their illness, and several near death claimed to find a new source of meaning and purpose at the end of life by sharing their stories.

Patient interviews addressed the patient's illness history, treatment history, personal perception of the treatment plan, perceived needs and desires regarding communication with physicians, and other thoughts or feelings they wished to volunteer. We were particularly interested in examining patients' perspectives on their communications with physicians and their perceptions of obstacles to their receiving the best care for their terminal illness. Our protocol was reviewed by the Department of Medical History and Ethics at the University of Washington School of Medicine and accepted by Hospice of Seattle. All patients provided informed consent before participating in the interviews. The thoughts and feelings of patients are identified, often by quoting patients' exact words. Pseudonyms have been used to protect the confidentiality of the participants described briefly in this report.

Case Histories

"Ann," a 34-year-old divorced woman, was diagnosed with breast cancer four years earlier. Surgical therapy was thought to have achieved a cure. A year ago, she had a recurrence with advanced metastatic disease for which she received palliative chemotherapy. In the past five months, she has had an abdominal operation for debulking of tumors and for lysis of adhesions, heart failure due to pericardial effusion caused by tho-

*See also "Clinical Management of Dying Patients" by J. Gavrin, MD, and C.R. Chapman, PhD, on pages 268-277 of this issue.

racic metastases, and surgical placement of a permanent pericardial drain.

"Bob," a 61-year-old retired seaman who lived alone, was diagnosed with colon cancer 5½ years earlier. His treatment with surgical and radiation therapy was thought to have achieved a cure. Two years ago, the cancer recurred with advanced metastatic disease in the liver, lungs, and bones.

"Fay," a 65-year-old woman diagnosed with colon cancer 2½ years earlier, had thought her irradiation and chemotherapy had achieved a cure. A year ago, she was found to have metastatic liver disease.

"Jon" is a 75-year-old retired electrician who is widowed and living with his son. Two years earlier he was diagnosed with lung cancer. Surgical treatment was thought to have achieved a cure, but seven months ago he was found to have advanced metastatic disease. He suffers from insomnia and cachexia.

"Ken," a 72-year-old married, retired aeronautical engineer, was diagnosed with cancer of the left vocal fold 11 years ago. Treatment was thought to have achieved a cure. He had a recurrence six years ago, and laryngectomy was thought to be curative. A year later cancer was found in his pharynx. He refused curative radical surgical therapy and instead underwent several courses of palliative chemotherapy. Four months ago he chose to stop all chemotherapy for his advanced disease. He has a tracheostomy, a gastrostomy (for feeding), and tracheoesophageal fistulas. He communicates only through writing and facial gestures. His wife, Nan, is able to interpret his expressions and at Ken's request assists him in communicating.

"Tom" is a 66-year-old retired electrician who is widowed and living alone. Seven years ago over the course of a year he underwent an operation, radiation therapy, hormonal therapy, chemotherapy, and surgical castration for prostate cancer. He thought he had achieved a cure. Two years ago he was found to have advanced metastatic disease. Complications included spinal tumors that have left him paraplegic and several hospital admissions for life-threatening gastrointestinal bleeding episodes of unknown origin.

Disclosure—A Crisis

Each of these patients described the disclosure of their original diagnosis as a critical event. The knowledge that they were living with a life-threatening illness raised questions about whether they would die of the illness, whether they would suffer greatly from the disease or its treatment, and whether they would become dependent on others for their care. All of these patients were advised of treatment plans tailored to their particular needs, and each thought that caregivers had a strong and supportive interest in assisting them. This helped ameliorate the acute crisis phase. When the treatment plan was described as a possibly curative measure, these patients seemed to assume that a cure would be achieved and developed a positive outlook toward the future, thus reducing their anxiety.

Curative Care Period

The illness profile of each of the participants was initially similar. After the cancer diagnosis, all of the patients experienced a curative care period perceived at the time as a cure, followed by a period of time in which they were able to resume premorbid activities. For many physicians, these patients were not necessarily thought to be cured of cancer, but might better be described as currently not manifesting any signs of cancer and possibly cured. For these patients, the curative therapy appeared to remove them from the acute crisis stage of facing a life-threatening illness. These patients chose to think of themselves as cured.

This disparity of perception raises perplexing questions regarding physician-patient communication. How explicit should physicians be about the possibility of recurrence? What if a patient does not ask about recurrence? Is it better to allow patients to proceed through therapy with the highest level of hope? Can the power of suggesting that the cancer might return be a self-fulfilling prophecy by weakening the immune system of patients through the stress of worry and anxiety? Physicians in other cultures such as Italy and Japan are far less candid with patients to encourage a hopeful spirit in battling against illness.[14-16] In the pluralistic culture of the United States, we hold that physicians should be truthful and provide any information that is requested by patients and should also be respectful of patients who choose to limit the disclosure of possible future complications.

The recurrence of cancer defined the beginning of a new period in the illness. At this point, five patients entered the palliative period, or the chronic living-dying phase of their illness. Their experiences varied, however, in how and at what point in the palliative period they came to the awareness of their true status. Two, Ann and Fay, became aware of being in the palliative period at almost the same time their physicians did. Two, Jon and Tom, interpreted treatment following the diagnosis of recurrence as curative, only to learn at a later time that the treatment of recurrent disease was palliative. Ken refused a radical operation that was presented to him as a curative therapy. He understood that "cure can only come from surgery." On his own initiative, he gathered information (through visiting a patient who had undergone a similar procedure and procuring a professional second opinion) and decided that a surgical procedure would result in a level of functioning that was unacceptable to him. Therefore, with the support of his wife, he chose to reject his primary physician's recommendation for surgical intervention. He relates, "As long as there was hope for a cure, I was willing for anything, until the point I learned the surgery would take away too much." With this decision, Ken knowingly entered the palliative period. One patient, Bob, received a single dose of chemotherapy followed by only palliative care.

The Early Palliative Care Period—
'I Am Incurable'

When relating their experiences during the transition period from curative to palliative care, these five

patients described two distinct levels of awareness, each holding separate and important meanings for them. Ann was best able to articulate the difference between these two levels of awareness. She chose the terms "incurable" and "terminal" to describe the two levels in the palliative period that seem to coincide with the living-dying phase and the terminal phase described earlier. She defined the meaning of being incurable and terminal as follows:

Being incurable meant that I would have to live with it. I knew that I was going to die, but I regarded that as something in the future. I didn't know when that would happen. I was more concerned with living as much as I could, getting as much done with the amount of illness and discomfort that I had. Incurable meant that I had to face dying, but I could face it in the same sense that everyone does. We're all incurable, everybody dies, and I'm going to die just like everybody else. Terminal meant that I had less time. It meant that dying was now countable. It was now time to prepare myself to die.

Ann picked up the terms incurable and terminal from health care professionals as they defined her status in the palliative care period. Although no one defined these terms, she felt she had an intuitive awareness of their meaning. Yet, terminal illness, from the perspective of medicine, refers to an irreversible disease process that will lead to death, more synonymous with incurable. Ann seemed to use terminal to signify the imminence of death. Pumphrey and Eisman remind us of the following[17(p227)]:

[T]he clinician can expect patients to tune in to the verbal and nonverbal messages of those around them. These messages may be distorted in reception, hence the need for clarifying dialogue on a continuing basis.

We found in these interviews that patients and health care professionals often attached different meanings to the terms incurable and terminal.

Like Ann, the other four patients referred to a time during their illness when they knew that their cancer could not be cured but did not consider themselves "terminal" or imminently dying. Only Fay understood that death was imminent. Tom suspected that he had entered the palliative period as he was more frequently admitted to the hospital with various complications. His suspicions were later confirmed through explicit conversations with his physicians in response to his questions about the imminence of death.

Ann was the only one of the six who learned that she was incurable as the result of an open discussion that was initiated by her primary physician with whom she met after her recurrence was diagnosed by an orthopedist. Ann: "That's one of the things that I like my doctor for, because he was plain with me that I was incurable."

As a consequence of learning that their disease was incurable but not yet terminal, two patients chose a course of aggressive chemotherapy. Both justified the debilitating side effects of therapy with the belief that they were in more control of the disease process, and they could achieve greater longevity and decreased symptoms. Ann: "I was able to make a trade-off. I exchanged a year of my life in chemo for about seven months of fairly good quality of life." These patients appeared to accept the inevitability of death and to integrate this reality appropriately in their decision making. The patients' descriptions of being incurable in the early palliative period seem to match our earlier description of the chronic living-dying phase. It is clear that good communication is essential to assist patients in understanding their situation and making appropriate choices in keeping with their values.

The Late Palliative Care Period—'I Am Terminal'

To all these patients, the most important event in the illness was the point at which they understood that death was imminent. Each of the six was able to describe a particular conversation with health care professionals in which they became aware that death was near. Their experiences varied as to whether the information was conveyed in an explicit or oblique manner, whether the discussion was initiated by the physician or the patient, and whether the patient chose to actively pursue further information than was initially offered. Three of the patients (Bob, Tom, and Jon) were informed of the imminence of death in an explicit manner. Bob: "I was given one treatment of chemotherapy. One treatment only, then they stopped. A little after that, in an office visit, my nurse told me that they couldn't do anything. He said, 'You are a terminal patient.'" Tom's awareness came when his physician enrolled him in a hospice program.

Tom: Basically, my doctor didn't tell me very much to start with. The doctor who covers for him told me "this isn't the same as before, you could go at any time." He told me in about four different ways the same thing. And then my physician basically told me to get things in order. He said, "You may have up to two years. . ." but he didn't really mean that I could have up to two years. *Question:* He didn't? How did you pick that up? *Tom:* Because he'd talked to me before. . . . He had told me that this was much more serious than the others [hospitalizations]. Then he said, "Well, I'm going to call in the hospice nurses, and they'll be able to give you some help." And it's my understanding that they don't come in until you have about six months.

After a course of chemotherapy followed by irradiation, Jon chose to ask his physicians "point blank" what his current prognosis was. At the time, he did not realize that his treatment regimen was palliative rather than curative.

Jon: I did think my radiation oncologist was uncomfortable when I asked her . . . there was a hesitation, a little reluctance. I told her, "Now, I'm going to ask you the $64 question. How much time do I have left? What am I looking forward to?" And she said, "Six months to two years." I don't think my primary doctor was uncomfortable. He was the one that said 90% of the patients in my condition don't, ah, last over six months. *Question:* You seem to be keenly aware of what was happening around you, and you responded by asking direct questions? *Jon:* It just kind of seemed to me that things fell naturally into place as we went along. As questions occurred, I asked them.

Fay's realization that death was imminent followed a single conversation with her physician. Although he had been explicit about the need for a palliative approach, he had never actually explained that her death was now imminent.

Fay: It happened so quickly. I just heard him talking to a nurse in the hall, and he said, "Let's call and see if we can get her into the program." That's the first I ever knew of hospice being around. *Question:*

After you heard them visiting in the hall, did he then come in and talk to you? *Fay:* Yes, he did. He explained the whole program. Instead of curing, going palliative. I didn't see what good any more chemo would do, or radiation or anything else. I figured that was it. So, here I am, in hospice. It's still hard to believe that this is available; it's great.

Ann described how she began to realize that she was terminal during a recent hospital stay.

Ann: Well, this last time that I went into the hospital, it was made plain to me that I was terminal. I mean, I knew that I was incurable, but I stepped over the line to terminal. *Question:* Was it any one physician that approached you and explained? *Ann:* No, the only way it was introduced to me, that I was terminal, was very obliquely through getting my codes. This doctor asked me, "What code do you want to be?" And I said, well, what does that mean? And he explained it [do-not-resuscitate order, or DNR code] to me. So I began to realize, even though it wasn't clear to me until a few minutes later, after the doctor had left, when I asked the nurse who had been there, why are they coding me? She said, "Well, you are terminal now." So the realization was partially there, but the nurse made it concrete, and that helped me.

We learned from patients like Ann that it is important to be informed of this change in their status so they can make plans for their remaining time.

Ken and his wife, Nan, chose to end chemotherapy when it seemed ineffective, leading to an increased awareness that the end of life was near.

Ken: I quit chemo because it was making me sick three days a week and there was no change in the tumor. I told my oncologist, and she agreed that my decision was valid because we weren't accomplishing anything. She had been proposing more and different types of chemo, but without too much enthusiasm. *Nan:* I think that the medical profession knows it's the end of the line, but they don't come out with it. They feel that they have to keep going or they aren't doing their job.

Ken and Nan describe a kind of technologic imperative, the pressure to use any therapy available, even if it may provide little or no benefit. At this point Ken decided to enter the hospice program.

Ken: I said to the nurse, "Is this the time to go to hospice?" The nurse said, "We think that's a very good idea!" In the end, Nan had to sign the papers because the doctor was unavailable. One of his staff told me, "He's very uncomfortable with patients who are dying."

Nurses were seen by these patients as more comfortable talking about death and dying:

Ann: Talking with nurses has helped a lot. I get tremendous support from them, but I don't think it makes up for talking to my doctor. It's frustrating, because these are excellent doctors, yet they can't talk about dying. . . . It's great being able to talk with the nurse, and I appreciate it, but she's not my doctor officially telling me, "You're terminal, you have to deal with this."

An awareness of imminent death encourages patients to put their affairs in order, provides an opportunity to openly communicate with those most dear, and allows treatment decisions congruent with patients' values.[18,19] All the patients interviewed were able to describe activities of a personal, practical, or interpersonal nature that they chose to undertake as a result of having become aware that death was near. Tom described working through his thoughts with the help of a friend, claiming, "I made peace with my life." Jon traveled to spend time with each of his children and their families while he still had the strength. After Ann became aware that death was imminent, she wrote her will and proclaimed, "Death is a practical business, as well as an emotional one." She went on to say

I was very grateful to know that I was terminal because it allowed me to spend some precious time with my family and friends that I might not have had if I hadn't known I was under the gun. My friends would ask when they should visit, and I could say, come as soon as possible because I don't know how long I'll be coherent. I'd rather have you with me now.

These patients described their need for candor on the part of their physicians, particularly at that point when the physician becomes aware that death is imminent. All preferred to learn this information from their physicians and wanted the information to be given in an explicit manner. They were unanimous in feeling that once the basic information had been provided, the physician should "open the door" for them to talk about any questions or issues they deemed important. Ann provided an example of how she would like to have been told:

He might say, "The cancer has moved into your chest. Do you realize that this means you have a shorter time? You're now regarded as terminal. Do you have any feelings about that or any questions? Is there anything you'd like to tell me?"

Each patient reported that accepting information about the imminence of death would be easier if it were presented with sensitivity and compassion. All acknowledged the difficulty of becoming aware of their impending death. As Fay said, "You hate to face that day." As Bob pointed out, however, "You can tolerate that difficult situation if you have a doctor who can sit down and explain and tell you where you are." These patients affirm the point that the psychological suffering of patients in the terminal phase of illness can be mitigated in part by the honest, open, and caring attitude of caregivers.

Summary

Although health care professionals possess an understanding of the pathophysiology of illness, its treatment and progression, patients often do not, and they look to their attending physician for appropriate and timely disclosures of information. Our discussions with patients confirmed that the initial disclosure of a life-threatening illness precipitates a crisis as the patient begins to contemplate an untimely death. We found ample evidence, however, that with compassionate support, comfort measures, and palliative care, patients move into a chronic living-dying phase that they often describe as "living with an incurable illness." Patients uniformly wanted to know when treatment modalities were no longer efficacious and that the approach had turned the corner to a palliative model.

Further along, in the late palliative period, patients also wanted to know when death was imminent. The patients discussed here are much like other patients we have cared for facing death from heart disease, lung disease, the acquired immunodeficiency syndrome, or any other life-threatening illness. Most admit to having particular tasks to achieve in bringing closure to life as death draws near. Others describe the spiritual richness

they experience in their last days, savoring the moments and living with the intensity of knowing their time is limited. Physicians who manifest genuine interest in their patients as persons, who use appropriate touch in conveying empathy, and who provide adequate and timely information are regarded as an important source of social support. Conversely, patients experience barriers to communication if a physician is anxious when discussing dying, resorts to medical jargon and intellectualization to avoid a more personal contact, or when care is so fragmented that a consistent source of communication is absent. Further qualitative and quantitative research into patients' perspectives regarding their care and the quality of their communication with caregivers in the process of dying can enhance our efforts in providing better care.[20] Further efforts must be made to teach medical students and resident physicians about the care of dying patients.

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Understanding Cultural Difference in Caring for Dying Patients

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Experiences of illness and death, as well as beliefs about the appropriate role of healers, are profoundly influenced by patients' cultural background. As the United States becomes increasingly diverse, cultural difference is a central feature of many clinical interactions. Knowledge about how patients experience and express pain, maintain hope in the face of a poor prognosis, and respond to grief and loss will aid health care professionals. Many patients' or families' beliefs about appropriate end-of-life care are easily accommodated in routine clinical practice. Desires about the care of the body after death, for example, generally do not threaten deeply held values of medical science. Because expected deaths are increasingly the result of explicit negotiation about limiting or discontinuing therapies, however, the likelihood of serious moral disputes and overt conflict increases. We suggest a way to assess cultural variation in end-of-life care, arguing that culture is only meaningful when interpreted in the context of a patient's unique history, family constellation, and socioeconomic status. Efforts to use racial or ethnic background as simplistic, straightforward predictors of beliefs or behavior will lead to harmful stereotyping of patients and culturally insensitive care for the dying.

(Koenig BA, Gates-Williams J: Understanding cultural difference in caring for dying patients, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:244-249)

In providing care at the end of life, a salient category of difference is cultural variation, which in the United States is usually understood as reflecting differences that divide along lines of race or ethnicity and, to some extent, religion. Death is inevitably understood and experienced within a complex web of cultural meanings.[1-3] How should physicians take culture into account when providing medical care for patients nearing the end of their lives?*

We focus on two questions: How does culture shape the experience of illness and death in clinically meaningful ways, such as mediating the response to pain? and How is cultural difference relevant to implementing the new "bioethics practices" that govern end-of-life care in US health care institutions? Practices such as writing do-not-resuscitate orders have become central rituals of death in our society, replacing other markers of transition from life to death.

Central to our discussion is a strong argument about the complexity of cultural interpretation and the need to draw clear distinctions between culture, race, and ethnicity as categories of difference. Dangers exist—for example, creating negative stereotypes—in simply supplying clinicians with an atlas or map of "cultural traits" common among particular ethnic groups.

Two Case Vignettes

As medical anthropologists, we have done research on how culturally diverse patients with cancer, their family members, and their health care providers have approached decisions about care at the end of life.[4,5] The following case vignettes, collected through in-depth interviews in the course of longitudinal anthropologic research, reveal the complexity of cross-cultural medical care.

Patient 1

A diagnosis of pancreatic cancer led this patient's care providers to initiate discussions about her resuscitation status on five separate occasions during the last months of her life. A note written in her medical record during a hospital admission for pain control stated: "Pt urged to consider DNR/DNI [do-not-resuscitate or do-not-intubate orders] given her horrible prognosis." But the patient persistently resisted her care professionals' view of what her course of illness should look like. A 46-

*Many of the issues addressed in this article are discussed in the September 1992 special issue of THE WESTERN JOURNAL OF MEDICINE, "Cross-cultural Medicine—A Decade Later," edited by Judith C. Barker, PhD (1992; 157: 247-374).

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year-old African-American woman with strong religious beliefs, she rejected "meals on wheels," refused hospice, and until right before her death, wanted cardiopulmonary resuscitation in the event of cardiopulmonary arrest.

The patient described the following exchange with a physician after her diagnosis, established with great difficulty after several procedures, was finally confirmed:

> But they told me—asked me did I want them to tell me how long I had to live. I told them no, because I said only God has priority over living. That's something man can't tell you—how long you got to live. I said only God can heal you. And they looked at me so funny.

The patient's physicians were compassionate, even visiting her at home during one attempt to verify her resuscitation status. But her medical management was complicated by fragmented care; her only insurance was Medi-Cal (California's Medicaid), and she had not seen a physician for more than five years before being diagnosed with cancer. In the end, frail, immobile, and full of ascites, she was cared for by a large extended family. Her efforts to manage her pain may have been complicated by her fear that medications sometimes "disappeared." Administrative hurdles set up by Medi-Cal made it difficult to get her prescriptions filled. Whereas from her physician's point of view, getting the do-not-resuscitate order was the key decision the patient faced, she was concentrating on getting well.

Patient 2

This patient was diagnosed with locally invasive nasopharyngeal cancer in China before he emigrated to the United States with his family. The oldest son, who attends college, always accompanied his monolingual father to the clinic. Despite treatment with irradiation and chemotherapy—along with traditional Chinese medicine—the cancer progressed to the point of being immediately life-threatening due to hemorrhage. Although aware of the nature and severity of the diagnosis, family members avoided the use of the word cancer, preferring the more neutral Cantonese term for tumor when discussing the patient's illness. The family's ideas about appropriate disclosure varied from the health care team's view. The patient's son complained, "For us Chinese, we are not used to telling the patient everything, and patients are not used to this either. If you tell them, they can't tolerate it and they will get sicker."

During one visit to the clinic, the physician wanted the patient's son to explain that chemotherapy had not been effective in his case and that there were no more treatments available. The son became distressed.

> I did not want to translate this to my father, but the doctor insisted on telling him everything. The doctor found the Chinese-speaking nurse to translate for him and told him everything.

Because of the family's reluctance to discuss the prognosis openly, the team's well-intentioned efforts to manage the patient's death at home were thwarted.

These case presentations reveal a range of ways in which culture is relevant to terminal care. Patient 2's use of Chinese herbal medicines in combination with biomedical therapies represents a successful blending of traditions. The two cases also show the potential for serious disputes and dissatisfaction when patients from a minority group are confronted with practices routinely accepted within US biomedicine. The patient's son did not share the high value his father's physician placed on open disclosure of a cancer diagnosis and limited prognosis. Patient 1 did not comprehend her physician's view that further treatment of her illness, including resuscitation, was futile.

Race, Culture, Class, Ethnicity—The Nature of Difference

Patient 1's race varies from that of most of the physicians who cared for her. Patient 2's ethnicity derives from his country of birth, his language, and his immigrant status. What do these categories mean, and how do they intersect with culture and with social class? One distinction—that the designation "race" reflects biologic difference whereas "ethnicity" refers to cultural variation—is outmoded. Adopting the term ethnicity was a change from 19th-century conceptions of race (or biologic variation) as the bedrock of difference. Although the word "race" remains in popular use, as a scientific classification it is based on "outmoded concepts and dubious assumptions about genetic difference."[6(p248)] Genetic variation within races is always greater than variation between races.[7] Races do not exist as natural categories; rather, they are social constructions, meaningful only within particular historical contexts, and subject to change.

In the United States, cultural and social class differences are often confused because ethnicity and class are closely correlated. Culture is not reducible to class, however. (A full discussion of the culture concept is beyond the scope of this review.) The medical anthropologist Arthur Kleinman explains how the concept has evolved and changed[8,9(pp113-114)]:

> Culture is now viewed not merely as a fixed, top-down organization of experience by the symbolic apparatuses of language, aesthetic preference, and mythology; it is also "realized" from the bottom up in the everyday negotiation of the social world, including the rhythms and processes of interpersonal interactions.

We focus here on interpretive approaches, on "reading" patients, as opposed to thinking about culture as a demographic variable that predicts specific behavioral traits. Gender differences must be approached in similarly sensitive ways. Culture is constantly redefined and negotiated, meaningful only when interpreted within the context of a patient's unique history, family constellation, and socioeconomic status.

Considering culture as a predictive variable is inherently limited—that is, simply plugging race or ethnicity into a multiple-regression analysis or, in a clinical context, assuming someone's name, appearance, or national origin is a predictive factor. The image that comes to mind is of a young medical resident, recently returned from a lecture on cultural sensitivity in health care, who pulls his or her index card from a pocket when dealing with a patient like patient 2 and, assuming that there

is no need to discuss his care directly with him—because Chinese culture is family-oriented—concludes that the resident's only responsibility is to follow the son's wishes.

Changing Demographics

As the United States becomes increasingly diverse, situations often occur in which the cultural background of a physician or other health care professional differs from that of a patient and family.[6] According to the 1990 census, the percentage of foreign-born residents in the United States is 8%. In the state of California, that figure has increased to 22%, with a concentration in urban areas. A third of residents of San Francisco and Los Angeles, for example, are foreign-born. In the United States, 12% of the population identifies itself as African American. Dramatically changing demographics offer only a partial explanation of the urgency of respecting cultural differences in clinical work. Equally salient are the political forces of multiculturalism.[10] The call for the recognition of minority voices in US society will inevitably surface as a serious concern during discussions of ethical issues in end-of-life care, particularly the appropriate allocation of ever-scarcer medical resources.

Cross-cultural Variations in Death and Dying

The culturally constructed boundaries between life and death are more variable than scientific definitions, based on cellular death or organ system failure, suggest. In Vanatinai, a small island close to Papua New Guinea, those who would be considered unconscious by western-trained physicians are viewed as already dead, leading to cases where a person may "die" many times.[11]

Similarly, cultural practices at the beginning of life shape the definition of death. In some traditional Native American societies, an infant was not considered a full member of the community until a "naming ceremony" or other ritual is performed, often at 1 month of age or older.[12] If an infant dies before this important ceremony, no funeral is required because the infant is not yet a part of the social group and hence not fully alive.

Death is socially constructed in the United States as well. The life of a bedridden, isolated, demented elderly woman could be described as a form of social death that precedes biologic death. Our familiarity with existing social definitions of life and death disguises the strangeness of a concept such as brain death. In the past three decades, the relationship between biologic and social death in the United States has been transformed by the new concept of brain death. Perhaps not surprisingly, this new construction has not been universally embraced. Empirical evidence documents a lower rate of organ donation by minority groups in the United States.[13,14]

The response to the loss of particular persons also varies considerably through time and place. In the contemporary United States, the loss of an infant or child is considered one of the most tragic experiences a family can face. By contrast, in less economically privileged societies, the loss of the family's primary worker may be much more tragic. In the northeast of Brazil where anthropologist Scheper-Hughes studied impoverished mothers, child deaths, which happened frequently, were understood to be inevitable, a function of the child's will to life; mourning lasted only a few days.[15]

Emotional expressions of grief are also highly culturally patterned. Although some form of ritual or ceremony to mark a death is universal, expressions of grief vary widely. Two societies that share the Muslim religion—Egypt and Bali—condone opposite expressions of grief. In Bali, a person in mourning must remain calm and cheerful, keeping a strict separation between inner and outer feelings. By contrast, in Egypt a woman who remains "withdrawn, mute, and inactive" for seven years while mourning the death of a child is considered sane and healthy.[16] In the dominant European-American tradition, both these patterns would be considered disorders.

A problem with blanket statements about cultural patterns is that they disguise the often important intracultural variation that exists in most societies and has always existed, even before the modern era of instant worldwide communication and massive migration. The notion that culture can be simply and easily "mapped" onto geographically isolated human groups has been abandoned by anthropologists.[17] Calls for "culturally competent care" ignore the dynamic nature of culture. It cannot be assumed that patients' origins will lead them to approach decisions about their death in a culturally specified manner.

Cultural Difference in the United States

Differences between nations are generally not ethically troubling for clinicians. That physicians in Japan or Italy choose not to reveal a diagnosis of cancer to a patient is not a problem if this is accepted and expected practice in a homogeneous society.[18,19] The situation in the United States is notably different. Maneuvering within cross-cultural encounters requires familiarity with the possible range of variation, both around the world and in the United States. Physicians need to know the possible range of variation in response to illness and death to respond to the needs of their patients.

In the care of dying patients, managing pain is often a central task. Sociologists have observed that the experience of pain and its expression varies among American immigrants.[20,21] Models have been developed that describe how cultural groups have different standards of appropriate behavior when in pain, which in turn lead to variation in how patients perceive, interpret, and respond to pain. More recent models integrate biologic, psychological, and sociocultural aspects of pain.[22] Researchers continue to demonstrate differences in how ethnic groups express and respond to pain, both acute and long-term.[23,24]

To understand the relationship between pain control and cultural difference, it is necessary to consider the historical and political context. Health care workers in urban clinics struggle with the issue of managing pain in an environment of poverty where drug abuse may be present. Social class-based divisions that separate the lives of health care professionals and patients are further accentuated by decades of overt racism and open discrimination. Pain management of Hispanic and white patients with similar trauma was compared in an emergency department.[25] Undertreatment of Hispanic patients in pain by health care professionals—perhaps because of overt discrimination—could not be ruled out, as later research showed that physicians were not simply making inaccurate evaluations of the amount and intensity of pain experienced by these patients.[26]

What constitutes a "good" death? As with the experience of pain, cultural narratives of dying vary. The ideal of hospice care, with its emphasis on a peaceful, accepted death at home in familiar surroundings with family members present, demonstrates unexamined white middle-class assumptions. African Americans have more negative attitudes toward hospice.[27] Admission to a hospice facility generally requires accepting the inevitability of death, expressed through the idea of a prognosis of less than six months to live and an agreement to forgo aggressive care and resuscitation.

Chinese immigrants may choose to avoid death at home because of traditional beliefs about ghosts inhabiting dwellings where someone has died. Indeed, a recent death may affect the market value of real estate in some Chinese neighborhoods (Evelyn Lee, EdD, oral communication, Richmond Area Multi-Services, San Francisco, California, June 1992).

Beliefs about the integrity of the body and its proper treatment after death are also areas of possible cross-cultural conflict. The idea of an autopsy may be repugnant to some groups, particularly if the request is made while the patient is still alive.[28]

New Rituals of Bioethics

Implications for Culturally Diverse Patients

Understanding that the experience of pain varies across cultural groups may lead to improved clinical management. More problematic is the observation that notable differences exist among cultural groups in the United States in accepting and using the bioethics practices that regulate end-of-life care. Inevitably, each ill person reaches a point when medical interventions can do little to stave off death and may, indeed, prolong the process of dying. Because expected deaths are increasingly the result of explicit negotiation about limiting or discontinuing therapies,[29] the likelihood of serious moral disputes and overt conflict increases. Negotiated deaths lead to bioethics rituals as a new rite of passage to death. In many American hospitals, the decision not to resuscitate a patient or to limit or discontinue therapy is the primary indication that the end of life is approaching. In a sense, because of changing medical technology, death has moved from the realm of nature to that of culture in our society. The cultural values and beliefs that inform the new bioethics practices are white, middle-class, and based on western philosophical and legal traditions that emphasize the individual and individual decision making.[30] Successfully implementing "death by decision" depends on a set of cultural attributes, including the open disclosure of distressing information, the desire for control, and future orientation, described elsewhere as the "autonomy paradigm" in bioethics.[31]

Surveys have documented the lack of fit between bioethics innovations and minority populations in the United States. Substantially fewer minorities make use of advance directives to guide their care at life's close. African Americans differ notably from European Americans both in their unwillingness to complete advance directives and in the desires about life-sustaining treatment expressed.[32] Substantially more African Americans and Hispanics "wanted their doctors to keep them alive regardless of how ill they were, while more . . . whites agreed to stop life-prolonging treatment under some circumstances."[33(pp157-158)]

A study comparing elderly persons from four cultural groups in Los Angeles found that 80% of Hispanics and Korean Americans endorsed the statement, "Life-sustaining machines should never be stopped because even if the patient appears to be dying, there is always the chance of a miracle." Fewer than a third of the European Americans agreed. The research demonstrated equally striking ethnic differences in beliefs about discussing death openly with patients; most Koreans and Hispanics believed that this was harmful to dying patients.[34]

An Individual Approach Versus Cultural 'Traits'

The challenge of respecting diversity is great. Because culture is fluid and dynamic, how can we respect differences while avoiding stereotyping of patients? The answer is clear. Patients should never be approached as empty vessels, as the bearers of particular cultures. Rather, it is essential to approach patients first as unique persons, assessing them within the context of their family or other key social support system. General knowledge about theoretical differences among groups is helpful. For example, it is useful to bear in mind that in many Asian societies, ideas about "selfhood" vary from the western ideal of an autonomous individual. A sociocentric or relational sense of self often leads to decision-making styles at odds with western bioethics ideals. Likewise, it is helpful to keep in mind that African Americans, with a complex history of limited access to services, may not trust physicians to act in a patient's best interest.[35] Nonetheless, clinical inferences about cultural difference must be evaluated for relevance to a particular patient or family.

We propose an approach with patients and families nearing the end of life. Rather than memorizing the traits

associated with different groups, we suggest evaluating each patient and family using the following guidelines:

- Assess the language used to discuss this patient's illness and disease, including the degree of openness in discussing the diagnosis, prognosis, and death itself;
- Determine whether decisions are made by the patient or a larger social unit, such as the family;
- Consider the relevance of religious beliefs, particularly about the meaning of death, the existence of an afterlife, and belief in miracles;
- Determine who controls access to the body and how the body should be approached after death;
- Assess how hope for a recovery is negotiated within the family and with health care professionals;
- Assess the patient's degree of fatalism versus an active desire for the control of events into the future;
- Consider issues of generation or age, gender and power relationships, both within the patient's family and in interactions with the health care team;
- Take into account the political and historical context, particularly poverty, refugee status, past discrimination, and lack of access to care;
- To aid the complex effort of interpreting the relevance of cultural dimensions of a particular case, make use of available resources, including community or religious leaders, family members, and language translators.

Politics of Multicultural Care

Assessing patients and families against the dimensions of cultural variation is an important first step. But in the complex setting of managed death, health care professionals have no guarantee that even the most skillful assessment will avoid or resolve conflicts, improve care, or eliminate dilemmas. Some adjustments to clinical management are relatively simple and straightforward. For example, it is relatively easy to respect the wishes of an Islamic patient and family who request that the patient's body be turned to face the east after death. This act does not interfere with clinical management before death, it is not offensive to medically trained staff, and it does not raise costs. Only a small adjustment in the routine of managing the body after death is required; respecting difference is easy because it does not challenge the physician's own values.

In direct contrast are those differences that create serious disputes and the potential for conflict. Like their patients, physicians act in accord with deeply held values; scientific biomedicine has its own set of "cultural" practices surrounding death and dying.

What of a family who requests indefinite life support for a brain-dead patient in an intensive care unit? Situations like this occur, demanding skillful clinical interventions while presenting complex policy dilemmas. The state of New Jersey has enacted revised brain death legislation that allows for an exemption based on religious beliefs.[36]

The ideal of respecting diverse cultural perspectives is based on deeply held American beliefs in the value of tolerance. This does not mean, however, that patients may demand unlimited treatment based on their beliefs or cultural identity. The challenge for clinical practice is to allow ethical pluralism—a true engagement with and respect for diverse perspectives—without falling into the trap of absolute ethical relativism.

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* * *

Talking to the Family

My white coat waits in the corner
like a father.
I will wear it to meet the sister
in her white shoes and organza dress
in the live of winter,

the milkless husband
holding the baby.

I will tell them.

They will put it together
and take it apart.
Their voices will buzz.
The cut ends of their nerves
will curl.

I will take off the coat,
drive home,
and replace the light bulb in the hall.

JOHN STONE, MD[c]
Atlanta, Georgia

From *The Smell of Matches* by John Stone
Louisiana State University Press, 1972

Caring for Patients at the End of Life

Accurate Prognostications of Death
Opportunities and Challenges for Clinicians

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Linking survival time to an array of prognostic variables through a powerful statistical model can provide reliable, valid, and potentially useful information for patient care. We present a summary of the recently developed SUPPORT model [Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment] for estimating survival time of seriously ill adult inpatients and illustrate the possible clinical use of such a model. This model is then translated into counseling. Clinicians are positioned to evaluate the relevance and validity of any model and to understand their persistent shortcomings.

(Lynn J, Teno JM, Harrell FE Jr: Accurate prognostications of death—Opportunities and challenges for clinicians, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:250-257)

What tormented Ivan Illych most was the deception, the lie, which for some reason they all accepted, that he was not dying but was simply ill, and that he only need keep quiet and undergo a treatment and then something very good would result.

The Death of Ivan Illych
LEO TOLSTOY, 1886[1]

"Doc, if I am dying, don't use those machines on me!" This admonition is repeatedly heard by physicians. How are we to know that someone "is dying?" Most physicians are willing to forgo useless medical interventions when a patient is near death or to shape a plan of care so that it reflects an unavoidably grim prognosis. To accomplish that, physicians need a number of skills and tools, including accurate ways of estimating survival prospects. In this article we review current efforts in that regard and evaluate the challenges and opportunities they present to practitioners and patients.

Only a few decades ago, all physicians had to offer for prognostication was descriptions of the survival experience of a large group of persons who were defined by one characteristic: perhaps those newly diagnosed with a deadly illness or those who had reached a certain stage of such an illness. Such groups included a wide variety of patients, usually with no systematic way to sort them out. With the recent introduction of better computing and statistical tools, dramatically improved objective estimates of prognosis have become available. In general, objective estimates of prognosis rely on simultaneously modeling the relation of the risk of death with each of a number of patient and treatment characteristics. To be accurate, the modeling draws on the experience of many patients, usually numbering in the thousands. These models are proving to be accurate and stable across time and institutions.[2-6] Outcomes for groups of patients are used routinely in developing practice guidelines, comparing care systems, and describing physician practices. They are not often standard elements in the care of individual patients, however. Just as for any new drug or laboratory test, their usefulness should be critically evaluated, and practitioners need to understand what can be achieved with objective estimates of prognosis and what cannot.

Good decision making with patients relies on understanding a patient's likely outcomes with the alternative care plans that could be implemented and the patient's preferences among them.[7-13] Objective estimates of survival might prove helpful in understanding the likely outcomes. Some people are suspicious of computer-based estimates of survival solely from an unreflective distaste for impersonal machines taking on what seems to be an important task. An editor at *The Washington Post* called one system a "life and death" computer, giving it a sinister image ("The Life and Death Computer," January 5, 1992, C6). Physicians should set aside that image. The computer is only a tool for rapid information retrieval and analysis. The experience of previous patients is all that we ever have to draw on in forecasting the course of a current patient. Individual physicians are susceptible to a number of errors in estimating prognosis: bias from recent experience, overestimating or

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ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
SUPPORT = Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment

underestimating the importance of a variable, or self-fulfilling prophesying, for example. A statistical model that relies on computer analysis can often weigh the elements more accurately and usefully than projections that rely on the average experience of mixed groups or clinicians' personal experience. If having better estimates proves useful, physicians should be as willing to use them as to use a better laboratory test or a more effective x-ray method.

What Can Be Accomplished With Objective Estimates of Survival?

The best that can be done with high-quality measures on a large population will not reveal the day that a person will die, and it probably will not limit the range of days to the next few, except in cases of persons barely surviving. This is because the pace of dying is affected by many factors over a substantial period of time. Prognosticating will always be inescapably difficult. Dying can be seen as a walk on a long tightrope. Measures of a walker's skill (the illness and the body's response), the gustiness of the wind (the rate of "external" events such as pneumonias and falls), and the nature of the assistance available (medical, nursing, and family care) will allow a prediction of how long the walk will go. But any such prediction is bound to be expressed in probabilities, as if the tightrope walker could start out many times, sketching out a curve of "time to fall" (time to death). An accurate prediction will entail expressing it as probabilities of attaining each successive meter on the rope (each successive time period). The likelihood of making it to each point is important and so is the variability around the estimate (a confidence interval around the survival curve).

Prognosticating those who are virtually certain to die or to live for the time interval of interest is generally obvious to a physician. The patients whose futures are difficult to discern are going to have less extreme prognoses. Models of prognosis are most important when the optimal care of a patient requires knowing whether survival likely lies above or below a treatment threshold. The same considerations apply as in evaluating the merits of a diagnostic test. The test is important only if its result would make it clear that a patient is beyond some individually determined treatment threshold. In the case of dying persons, the "treatment threshold" may be the survival rate at which a patient finds it worthwhile to endure more life-extending therapy or at which it becomes obvious that a patient's concern for spiritual solace has become paramount. We have shown, for example, that patients with a less than 1% likelihood of surviving for two months often have ventilators and other life-sustaining treatment withheld, indicating that this is often below the clinical threshold now in use for continuing aggressive care.[14]

Careful readers will have noted that we have defined a "treatment threshold" that grows from a patient's clinical situation and preferences. This is different from the use of statistical cutoff points below which the use of certain treatments is to be barred to constrain expenditures. The latter application of prognostic statistics is, and should be, controversial. Sustaining such a fixed cutoff point would require broad consensus on the trade-off between public welfare and individual loss. At the very least, statistical prognostication should be applied as fixed cutoff points only when the issue has been publicly disclosed and debated and when patients and families have had reasonable notice. This is too important a matter to be decided arbitrarily or secretly by insurers or managers, or even by physicians. Furthermore, the more acceptable a cutoff point may be, the less effect it will likely have on costs,[14] in part because current prognostication reflects current clinical care patterns that include patient-centered thresholds. In fact, if we arbitrarily cut off treatment for certain patients with bad prognoses, that change will alter the statistical prognostication itself by making bad prognoses worse from lack of treatment.

A prediction of survival can be expressed at least two ways: as a probability of surviving a certain period of time or as a median survival time. What is possible to say is that, for 100 people who are exactly like this person insofar as measured by the elements that are included in the model, the number expected to be alive at the target time is n, or the average or median survival time is t days. Each of these can be bounded by confidence intervals that reflect both the amount of evidence used to develop the prediction (sample size and follow-up duration) and the unexplained variability in outcome from patient to patient.

Practitioners must be familiar with the interplay between the prognosis for survival to a given time and the prognosis for median time to death. Sometimes a prognosis sounds almost encouraging when stated: "The patient has a 1% chance of making it for two months." The same patient would have a median survival time of one day.[14] Table 1 gives the equivalent statements for patients in the SUPPORT project (Study

TABLE 1.—*Relation of 2-Month Prognoses and Median Expected Date of Death for Patients With Acute Respiratory Failure or Multiple Organ System Failure With Sepsis in SUPPORT (n = 3,515)**

Prognosis at 2 Months, % Survival	*Median Days Until Death*
90	>4.6 yr
50	60
20	13
10	9
1	1

SUPPORT = Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment

*Maximum follow-up, 4.6 years.

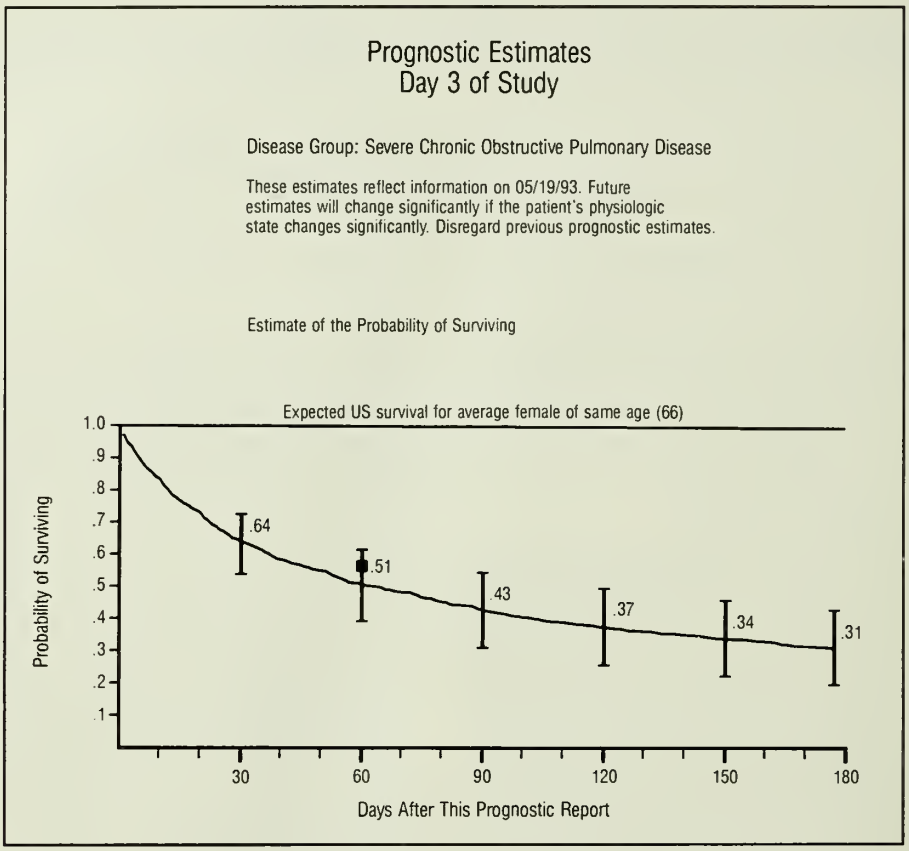

Figure 1.—This example of a prognostic estimate on the 3rd hospital day for a SUPPORT patient with severe chronic obstructive pulmonary disease shows the likelihood of survival on every day through 6 months, along with the 95% variance bounds and the effect of including an attending physician's prognosis as a data element. SUPPORT = Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment, ■ = model estimate enhanced by physician's estimate is .57 (95% confidence interval, .46 and .66)

to Understand Prognoses and Preferences for Outcomes and Risks of Treatment)[6] who were enrolled with severe acute respiratory failure or multiple organ system failure with sepsis.

An optimal model requires including measures of variables that might affect survival, usually as drawn from clinical experience and preliminary research. These variables should be specified in advance of data collection and should have a discernible path by which to affect survival. An optimal model will be one generated from the population in which it will be applied. Applying models farther afield will always entail some uncertainties. We will return to an explication of how to assess prognostication models. A characterization of one such model will serve as an introduction.

The SUPPORT Survival Time Model

In the SUPPORT project, we developed a prognostic model (Figure 1) that predicts survival time of patients identified in hospitals with a defined level of one of these serious illnesses: acute respiratory failure, multiple organ system failure with sepsis or malignancy, coma, chronic obstructive pulmonary disease (COPD), congestive heart failure, cirrhosis, colon cancer, and lung cancer. The steepness of the curve is determined by the class of disease (chronic, acute, or malignant cancer). The overall placement of the curve is determined by the severity of the disease, as expressed in the 14 variables that are measured to generate a curve like this for each patient.

The variables included in the final model were the diagnosis, serum sodium level, temperature, respiratory rate, heart rate, oxygenation, creatinine level, mean blood pressure, bilirubin and albumin levels, Glasgow coma score, age, days in hospital before becoming eligible for SUPPORT, and having cancer as a co-morbidity. The model uses the most abnormal measured value during a given day. These variables are all available in the medical record and are commonly measured in hospital patients. The model generates a point estimate of the chances of surviving to each day and an estimate of the variation around that point (which is a function of the number of patients and the accord that they evidence in regard to the optimal weighting of each element). This model generates a unique curve for each patient on each reporting day, resting on that patient's specific vital signs, laboratory values, diagnoses, and experience.

Variables were allowed to take nonlinear forms and were entirely prespecified as being likely to have importance in prognosticating survival time. As distinct from clinicians, the model is not swayed by recent experience nor biased by clinical "rules of thumb." Instead, it is fitted directly from the data.

Clinicians might still find it less than satisfying. Certainly, patients' physicians know more than 14 things about their patients, and some of them are important in prognosis. Likewise, physicians know more about what treatment will be used, whereas the model must expect "usual" treatment.

In SUPPORT, the model was generally as accurate as were attending physicians, making fewer extreme errors but being a little less discriminating (see below for an explanation of these terms).[6] Most important, we found that adding the objective model to a physician's own estimate actually made a model that was much better than either alone. The statistical model builds on a database that is far larger than any one clinician's experience, and it allows no psychological errors. The physician knows more about any one patient, however, including some elements of the treatment approach that might affect prognosis. Of course, physicians are sometimes biased in various ways, including enthusiasm for new treatments. The model that predicts outcome most accurately is one that uses both physiology and physicians' estimates, and the best use of any model requires physicians' interpretations of the model's estimate.

Clinical Counseling

Obviously, the counseling of particular patients must take into account a host of emotional and social matters. Nevertheless, we will articulate here just the components of that counseling that arise from estimates of likely survival for a patient with severe COPD who is debating whether to forgo any future use of a mechanical ventilator. We do not put this forward as an optimal format, but only as legitimate and possibly useful elements. Any real discussion would have much more input from the patient, and the physician's words would be responsive to the patient's language, concerns, and interests. The following monologue would never properly be given in this format, but it illustrates the possible content.

Example

Mr Jones, you have been asking to know more about how the last stages of this disease are likely to unfold. I know you don't want to go back on a breathing machine if you are not likely to live long anyway. I can tell you how other patients with your disease have fared. You'll have to help me decide what that means for how we should handle the situation when you again become short of breath.

If we had 100 patients exactly like you, with your disease and age and all the same lab values, you should know that half would have died by the end of two months. However, there would be 10 who were still alive at six months, and 1 would make it a full year. On the other hand, 10 of our original 100 would have died in the next ten days.

Now, our best information is based on careful study of about 500 people with very bad lung disease, all treated at teaching hospitals. We could be more confident in these estimates with more study, of course, but I don't think we'll find that the time it takes to lose half of our original 100 will be in error by more than two weeks.

Evaluating a Model to Predict Survival and Applying It to Individual Patients

Using objective estimates for patient care raises different problems and possibilities than using them for research (such as to correct for disease severity in comparing groups) or for public policy (such as to monitor effects of a change in policy on survival). These latter uses are well established and rely on the model performing well in most cases and similarly in comparison groups. Its use in clinical medicine requires that the model perform well for particular patients. The latter use requires a generally more exacting standard and thoughtful clinicians.

Of course, clinicians need not stand alone in this evaluation. The first two questions below will usually require some evaluation of individual patients, but the last three are more generic. These might well be evaluated by peers in professional publications or by professional societies, such as the Clinical Efficiency and Assessment Program of the American College of Physicians, or by more local or regional practice groups.

The following five elements are central to determining whether a model developed to predict survival is applicable to a particular patient situation:

- Were the patients used to develop the model similar to the current patient?
- Was the survival end point the one that matters to this patient?
- Were the predictor variables reasonable, appropriate in number, measured reliably, handled well, and characterized adequately?
- How was accuracy of the model quantified?
- Has the model been validated in an unbiased fashion?

Were the Patients Used to Develop the Model Similar to the Current Patient?

Applying predictive models to a new patient is safest when the patient is similar to the population used to make the model. The current patient is ordinarily separated from the latter at least by the passage of time. The patient also is usually not in the same care system, not in academic hospitals, or not of the same ethnic and genetic heritage. If the modeling stratifies patients into large groups (those with a certain extent of cancer), the current patient might be pushed into a group from which he or she is dissimilar because there were few patients with the particular combination that this patient exhibits. If the modeling comes from a randomized clinical trial, the entry criteria are often restrictive (many actual patients would have been excluded because they would not have consented to randomization). Some models have been tested or developed in enough environments that the

variation induced by disparate institutions is described, but that is uncommon.[4,15,16] More often, the practitioner will have to reflect thoughtfully on the likely differences between the population used to generate the prediction model and the current patient, considering both whether the disparities are so substantial that the model is irrelevant and, if not, what sort of corrections might be appropriate to apply if it is to be used.

Was the Survival End Point the One That Matters to This Patient?

If the clinical situation turns on survival for two months, a model to predict survival to hospital discharge may not answer the need. If the clinical situation turns on getting home, a model to predict survival for six months may be rather imprecise. The most useful models are those that predict survival over time or to the end points that a patient needs.

The outcomes of relevance need to be measured exceedingly accurately. A model that is constructed with a large number of persons lost to follow-up has serious risks of being unreliable, especially if the reasons for loss are not known. With the development of the National Death Index in the United States, this problem should be confined to the rare populations for whom personal identifiers are themselves difficult to obtain.

Were the Predictor Variables Reasonable, Appropriate in Number, Measured Reliably, Handled Well, and Characterized Adequately?

The most important decisions in formulating a prognostic model are selecting and measuring the predictor variables. First, which variables are tested as predictors of survival is critical in model development. Variables should reflect what is known of the cause and the course of an illness. In comparison with the array that a clinician thinks is likely to be important, the model may report a limited list. This often arises in analyses of data that were collected for some other purpose and that simply did not collect some key predictor variables. A model that predicts mortality from previous hospital utilization and "diagnosis-related group" for billing is obviously likely to perform less well for many clinical situations when compared with a model that also includes measures of physiologic function and disease severity. Sometimes variables indicating chronic physiologic dysfunction or deficient nutritional reserve (such as serum albumin level) are extremely important prognostic factors. Practitioners should again consider what elements of a clinical situation seem likely to be relevant to prognosticating survival and should be suspicious of a model-building process that did not test all of those elements.

Second, clinicians should ask whether the research that generated the model included too few patients to test the number of variables. Testing too many variables results in "overfitting," a situation in which the model works well only for the particular group that generated it. As an approximate rule of thumb, practitioners should be suspicious of any model that had fewer than 10 to 15 dead patients for every variable that is tested (counting nonlinear and interaction terms and counting every variable tested, even if it is not in the final model).[17] If a model is built on too small a database, clinicians cannot know what elements will be misleading.

Third, data on a large number of patients are likely to be missing. In retrospective studies, information is limited to what was written down at the time, and a missing laboratory value or vital sign is irreplaceable. Even in prospective studies, costs and ethical considerations may well limit how complete the data can be. How the missing data are treated can be important. Usually missing data are presumed to be normal, but this is potentially misleading because many patients who do not get those items measured would have evidenced substantial abnormalities. Sometimes missing data can be more accurately input from other variables, or a measure from a different respondent or test can be substituted. Clinicians should look for and evaluate a model's handling of missing data.

Finally, sometimes a predictor variable is used that is not readily measured in a particular patient. If it is important in the model and it cannot be estimated from measurements that are possible to do, then the model is not helpful to a particular patient's situation.

In sum, clinicians proposing to use a predictive model will need to see that the variables being used to predict are a reasonable array of the elements that should have a role, that they are measured well and handled well when missing, that the number of patients needed to develop the model was appropriate to support the model's complexity, and that the measures are ones that can be replicated in the current patient.

How Was Accuracy of the Model Quantified?

A model to predict survival has two major dimensions of accuracy.[18] First, do real patients have the expected survival experience? Second, does the model separate patients along a continuum from those dying quickly to those surviving a long time, or those patients having an event versus those not having that event? The first is termed "calibration" and the second "discrimination." A model should be well calibrated: of 100 patients (P) at any estimated likelihood of survival, $100 \times P$ would be expected to survive. This is ordinarily illustrated by dividing patients into groups along the range of predicted survival and plotting the proportion who survived within each group against the mean predicted outcome in that group (Figure 2). This curve not only shows the general match of prediction and performance but also the ranges of probability in which the model performs less well. Again, practitioners should pay attention to a model's overall calibration and whether a current patient is in a range in which performance is regularly biased.

A model's discrimination is its ability to separate those who die (or die early) from those who survive (or live a longer time). A general index of discrimination is

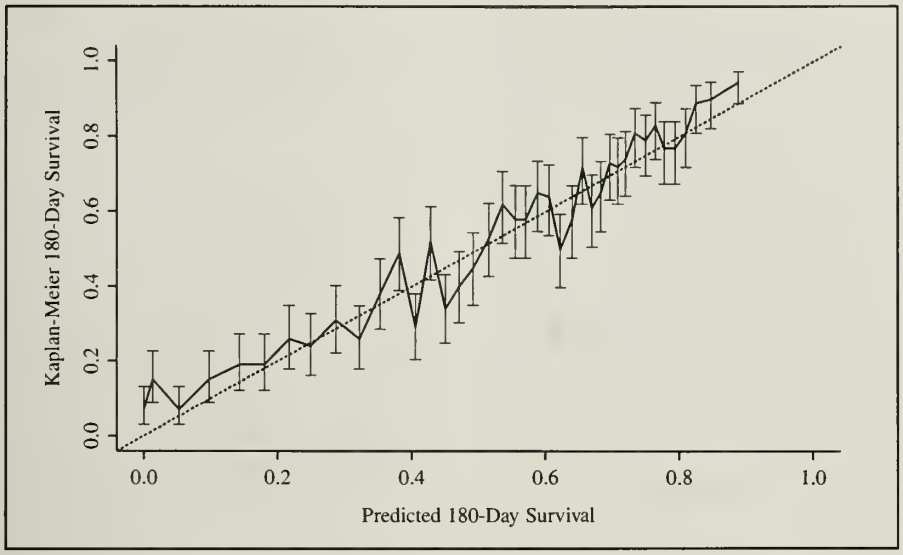

Figure 2.—The calibration curve for the SUPPORT [Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment] prognostic model shows a close fit across range of prognoses (n = 4,028; 1,889 died) (from Knaus et al,[6] reprinted with permission).

the *c* index, where *c* stands for concordance. All possible pairs of patients for whom survival times can be ordered are examined, and the proportion of such pairs for which the predicted survival and observed survival are concordant (that is, in the same direction) is computed.[18] The *c* index can be easily converted to a Somers' D rank correlation index that quantifies the association between predicted and observed survival, using the equation $D = 2(c - 0.5)$. When the outcome is dichotomous (such as hospital death), the *c* index is the same as the area under a "receiver operating characteristic curve."[19] A model that has no discrimination ability has $c = 0.5$ and $D = 0$, whereas a model that perfectly separated high- and low-risk patients has $c = D = 1$. A model is typically deemed to be clinically useful if *c* is 0.8 or higher ($D \geq 0.6$) for binary outcomes. For continuous outcomes, lower indices are still worthwhile.

The difficulty in assessing a model's predictive accuracy is to avoid allowing overfitting to account for the model's performance (with respect to both calibration and discrimination). This is also addressed under the discussion of whether a model has been validated in an unbiased way.

For some clinical uses, the measure of importance is not the generalized performance of the model but its performance in regard to a specific threshold. If the threshold for subjecting a patient to an additional onerous but possibly valuable treatment is that the patient be more than 50% likely to be alive in two months, then the clinician needs to understand the model's discrimination around that threshold. If the threshold for stopping a ventilator is that the patient has no more than a 1-in-20 chance of surviving for a month, then what matters is the model's ability to discriminate at that end point, rather than its generalized performance. Such specific measures are only sometimes available in the literature but often could be generated from the original data or approximated from what is published.

Has the Model Been Validated in an Unbiased Way?

The most authoritative way to prove merit in a model is that it maintains its calibration and discrimination when it is applied to a different population that is similar to the one that generated the model. This test simultaneously accounts for problems with data and overfitting and enhances a practitioner's confidence that the model can be used in settings other than the original.

In the medical literature, the accuracy of a model is often assessed on the same set of patients who were used to find the important variables and to estimate the regression coefficients (the weights to be assigned to each predictor variable). This results in an inflated estimate of accuracy because of overfitting: fitting spurious associations in the data that are not likely to be replicated in future data. In extreme cases, a model with nine predictor variables measured in ten patients will perfectly predict the outcomes of those ten patients, no matter which predictors are used.

The first method of validation that a clinician should look for is an internal validation that corrects for overfitting. The most common approach is cross-validation, but bootstrapping has been shown to be much more precise. In bootstrapping, a large number of samples are taken (with replacement) from the original patients. For each of these bootstrap samples, a model is fitted using the same strategy that was used to fit the "final" model as reported. The resulting new model is then evaluated in both the bootstrap sample and in the original patient sample and the average disparities used to adjust the estimates of accuracy in the "final" model.[20,21]

Although internal validation shows that predictive accuracy does not come from overfitting, being sure that the model can be applied to new populations requires external validation. By estimating the calibration and discrimination accuracy of the model on a new patient series from another time or geographical location, a check is obtained on the entire process of variable definitions, measurement methods, patient entry criteria, and the fit of the model. A well-constructed model should lose no more than a few percentage points in its *c* index or Somers' D when it is applied to a new group. Losing much more should be a warning that the original model may be too closely tied to the original population, variable definitions, or measurement methods to be used in other settings.

Persisting Limitations on Objective Estimates of Survival

The most striking limitation is that existing models do not often account for variations in treatment. Instead, patients are assumed to be treated "in a typical way," and neither actual treatment nor choices about possible treatment (such as decisions to order no resuscitation) are entered into the formula. This is not because these decisions are thought to have no effect. Rather, it is difficult to discern how to include as predictive elements those aspects of care that regularly happen after a prediction is made. What might be wanted is to have two predictions: one for patients with a hospice-style supportive care plan and one for patients with a fully aggressive, life-extending approach on the first hospital day, for example. But these are changeable behaviors, rather unlike the immutability of age. Behaviors might well be changed after receiving an estimate of prognosis, and those changes in behaviors might alter the estimate itself. This possible "feedback" of treatment choices on estimates and predictor variables has been evaded in prognostic models to date by excluding elements that are clearly under human control. Nevertheless, the treatment plan probably does make a difference, at least sometimes. Practitioners will have to bear in mind that prognostic models to date reflect current practices, whatever they are, and a patient who is pursuing more, or less, aggressive care may have a different survival likelihood. If current treatment plans are biased to the disadvantage of some group (for instance, on the basis of age), that bias will affect predictions of survival as if the alterations resulted from physical processes rather than behavior.

Prognostic models are obviously more limited in the diversity of predictors than is actual clinical practice. Diagnostic labels reflect a major oversimplification, for example. A patient who has an unusual case by virtue of its cause or course will likely have a different experience than the usual person with this diagnosis, which is all that the model can estimate. We can, of course, develop gradually more precise categories and estimators, but there will always be a limit and thereby the need for physicians to note that a given patient's course is expected to deviate from the usual.

More troubling to clinicians is that many prognoses will forever be "intermediate," in the sense that the prognosis is neither so bad nor so good that it makes a decision obvious. We may succeed in gradually finding ways of enhancing discrimination of our models, but the natural variability of humans suggests that there will be a limit and that many people will be in a muddled middle ground of prognosis at a time when clarity in either direction would facilitate decision making substantially. Rather than being a failing of the modeling, this is a reflection of the finitude of what is possible. Once a model is constructed, though, application is so inexpensive that the marginal contribution of the information can be small in many cases and still be worth generating.

Whereas prognostic models are gradually more capably assembled and more adequately validated and reported, few have had their use evaluated in practice. Until that is done, we have to acknowledge that it is uncertain whether better prognostic information will improve outcomes for patients or society.

A Practical Approach

Physicians who regularly work with a population at risk of dying and for whom accurate models of survival are available should certainly know the characteristics of these models and generally for whom they will be useful. Such a physician will also have to develop skill in conveying the essential information to patients and families, many of whom will have difficulty understanding the uncertainties involved. But such a physician will have garnered a uniquely powerful tool. The model is largely immune from the errors that physicians are prone to make.[22] It "remembers" cases completely accurately, and it weighs the predictors with cold precision. These correctives are of value to physicians and patients. When a model's predictions are substantially different from those of a physician, a search for the reason can be illuminating. When a patient seeks the information, it can provide a solid anchor to what otherwise might be free-floating conjecture about a person's life span.

These are important and substantial uses that take predictive models out of the research and policy environment and put them into clinical practice. These models are not dictators, but only tools. They will be most helpful when well understood and thoughtfully applied, and their use warrants careful evaluation.

Hippocratic writers characterized the physician's role thus: "Declare the past, diagnose the present, foretell the future; practice these arts."[23] We should strive to do so; a contemporary Ivan Illych deserves to know his peril.

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Caring for Patients at the End of Life

Improving Care of Dying Children

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Every year about 5,000 children aged 0 to 14 years need hospice care in the United States. Children seem to know that they are dying, although this is difficult for parents to accept. Clear, empathic understanding is needed. Communication with clarity and understanding is imperative with the changes in goals from cure to palliation to comfort. The ideal place for most dying children is at home, where symptoms can be managed as effectively as in a hospital.

(Martinson IM: Improving care of dying children, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:258-262)

There are three possible treatment goals for children. Cure is the first goal. When cure is no longer possible, palliation is next. When dying is not immediate and the quality of a child's life is still good, procedures and medications may prolong that life. We will speak to the third goal, when comfort becomes the highest priority and the prolongation of dying is to be the only likely result of aggressive treatment. Comfort care is not euthanasia. Withdrawing procedures that have no benefit for a child is not euthanasia. Cure-oriented treatment can be futile. A dying child may actually live longer in a home environment than in a hospital.[1]

Clinical Issues in Terminal Care

Do Children Know They Are Dying?

Many investigators have provided the research base that changed the clinical practice of physicians, nurses, and other health care professionals caring for gravely ill children.[2-4] Their studies gave evidence that, indeed, children do know when they are dying. Some of the possible reasons that a child would know this are the loss of ambulation, energy, and enthusiasm; awareness of feelings and actions of others; the depression that may be sensed; and resting without feeling rested. Based on clinical experience, children seem to be more aware of physiologic changes in their bodies than are adults. Treatments have become increasingly complex, however; in fact, some treatments for certain cancers bring children close to death and then "rescue" them. Some children make amazing recoveries from the point of near death due to serious toxicity or complications of treatments, all of which make dying and the death event more difficult to predict.

How Many Children Die Per Year and Why Do They Die?

About 45,000 children aged 0 to 14 years die each year. We have estimated that 5,000 will need clinical hospice services[5]; Table 1 shows the conditions of 4,115 children who died in 1992 for whom such services might have been desirable.[6] According to the National Hospice Organization, 90% of hospices accept children, and about 1% of the 246,000 who die in a hospice or with hospice services at home are children, which is roughly half of the estimated population need (*National Hospice Organization Newsline*, October 1993; 3:1-2). There are about 35,000 infant deaths in the first year of life; it is uncertain how many would be eligible or appropriate for hospice clinical services.

What Should Be Done When Cure-Oriented Treatment Is Stopped?

Good communication between a health care team and parents and children is always important but becomes crucial when a child is terminally ill. At that point, health care professionals need to objectively step back and realize that a cure is no longer possible and that any further intervention will only have an adverse effect on a child's remaining time. They must then be able to communicate this to parents and the child. In an atmosphere of open communication, parents are encouraged to ask questions about treatments. It is the health care team's responsibility to make sure that parents understand what they are told. It is particularly important for physicians and nurses to listen to the child and other family members and to understand a family's concerns and priorities when attempting to shift the focus of care from cure to symptom control. Anger at health care professionals because they "gave up" and regrets or guilt based on misunderstandings are difficult to resolve after a child has died and may be barriers to resolving feelings around the death. Parents and family members must be able to look back and have a sense of peace because they "did the right things."

For most families, the decision to stop cure-oriented treatment for a child with terminal illness is usually made

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TABLE 1.—*Potential for Hospice Care in Children*†*

Age and Passible Haspice Care	*Cancer, Leukemia*	*Congenital Anamalies*	*Heart Disease*	*Pneumania and Influenza*	*Human Immuna-deficiency Virus*	*COPD*	*Accidents*	*Hamicide*	*Suicide*	*Total*
Aged 1-4 yr										
Possible hospice care	479	856	286	188	161	--	--	--	--	1,970
No potential for hospice care	--	--	--	--	--	--	2,467	--	--	2,467
Aged 5-14 yr										
Possible hospice care	1,105	448	284	104	104	100	--	--	--	2,145
No potential for hospice care	--		--	--	--	--	3,388	587	314	4,289
Total	1,584	1,304	570	292	265	100	5,855	587	314	10,871

COPD = chronic obstructive pulmonary disease

*Adapted from Annual Summary of Deaths, United States, 1992.[6]

†The more than 35,000 infants who die during the first year are not included in this table.

by the physician, with parental involvement at some level. Families should ask, "What are the goals for future treatment?" Whether to stop cure-oriented treatment is a major responsibility for health care professionals, and openness and willingness to discuss this difficult subject are imperative. Families should be encouraged to ask about the wisdom of continuing cure-oriented treatment whenever they have questions. I believe that families are requiring more information in this area than is usually given. When health care professionals do not handle this decision responsibly, the tragedies can be many.

The major communication difficulty between families and health care professionals occurs when the goals of treatment change from cure to palliative care. Physicians may think they have informed the family of the impending death and that cure-oriented treatment is no longer the goal, but the family may not understand the full import of the message. Technical language is a frequent barrier to understanding, as is physicians' unwillingness to repeat information and answer questions. A primary care nurse may have a role in these conversations in reaffirming the information that the physician has shared and ensuring that consistent information is given.

Dealing with the family during the final stages of a child's life is one of the most difficult situations that health care professionals find themselves in. Unfortunately, because of the nature of medical technology, health professionals may at times find themselves prolonging death rather than improving the quality of life. Health care professionals have an obligation to the families of patients to be honest and objective about their child's condition, treatment, and prognosis. This includes telling the family when it appears that further therapy is simply prolonging the child's dying, thus continuing and possibly increasing suffering.

Conversely, the meanings of such treatments as the use of steroids or irradiation for comfort rather than cure need to be made clear. It is imperative for parents and family members to understand that the goal of these treatments is for comfort care.

Although experimental therapies should be made available when appropriate, parents should not be made to feel obligated to commit their child to research protocols. The first obligation of health care is "to do no harm."[7]

Where Should a Child Die?

No child should have to live unnecessarily in a hospital. A number of research studies demonstrate that most terminally ill children, as well as their families, do better when the child is cared for at home.[8] The importance of parental attachment and nurturing of children must not be put aside because a child is dying. Facing the end of a child's life, families must be able to make the most of each moment together. The successful provision of home or hospice care for children does not occur without careful planning, however. Effective nursing case management, either through the hospital or the home care and hospice agency, can aid a smooth transition from hospital to home. Communication among the various health care professionals is extremely important and is often facilitated by a nurse. The child's and family's individual needs must be considered in discharge planning and in providing education and support for parents or other caregivers at home. Hospice care and other related services such as respite care are essential for most parents, but may not be covered by medical benefits or may not be available where they live. In some areas there are agencies dedicated to providing bereavement support and counseling for families of children with terminal illness. A nurse can help families to take advantage of such local community resources.

The physicians and primary nurses who have been the principal caregivers should try to stay involved with families and help make a smooth transition from hospital to home and hospice care. Hospice services are increasingly available throughout the country. With assistance and support by the personnel in the treatment centers, local community-based hospices or home care agencies can be immensely valuable in assisting families of dying children. Where hospices are not locally avail-

able, nurses with medical and nursing support from pediatric specialty treatment centers can assist a family.

What About Reimbursement?

Home care is effective in reducing the total costs of health care. But the economics of health care in this country have resulted in a lack of stable funding of home care for children. The funding for services varies among health care professionals and from state to state. Even when hospice care and other related services are covered by state Medicaid programs or private carriers, there may be no mechanism for helping parents access these services. If such services as 24-hour-a-day on-call nursing, respite care, and durable medical equipment for home use are not covered, the cost of these essential services may prohibit families from taking advantage of the basic hospice services that are covered.

Most parents would prefer to care for their children at home despite the tremendous amount of energy and time that is required. Because of economic problems, many children with cancer and other terminal illness live out their lives in hospitals, at great emotional cost to themselves and their families. In one study, the costs of hospital care were from 22% to 207% more than home care.[1] The variation in comparisons depends on regarding home care as an alternative to inpatient hospital care or a larger concept of care that included added services at a time when a child would not need hospital care.[1] More recent data have been reported from the Children's Hospital in Los Angeles on provider use and duration in a pediatric hospice program for 177 children retrospectively and for the families of 27 children prospectively enrolled in a pediatric hospice program.[9] The mean total cost for the families was $4,808 per patient; incidental expenses were $446 and indirect costs $1,478 (indirect costs include foregone earnings of the family, friends, or volunteers). These researchers concluded that children can be cared for at home whether or not they use hospital outpatient or intermittent inpatient care and whether or not they continue with aggressive therapy. They also showed that services can be made available to both single- and two-parent households from a wide variety of socioeconomic backgrounds. In another study, the median cost for children who died at home was $4,858 compared with $13,975 for children under traditional care.[10]

Managing Symptoms at Home

The best use of pain medication and compassionate concern for the physical, psychological, and spiritual well-being of a child and family should be the primary foci of the professionals caring for a dying child. Goals of treatment should be for the child to function to the maximal level of ability: being with the family, riding a bicycle, going to the grocery store, or attending school, as the condition permits and the child desires.

Pain. Although it is known that children experience the same degree of pain as adults, children are still frequently undermedicated for pain. Successful pain management involves 24-hour dosing, with "rescue dosing" as part of the treatment plan. Morphine, the most commonly used pain control medication, can be given by mouth, suppository, or through self-regulating intravenous infusion pumps. With the new infusion pumps by catheter, full pain control is possible with patient-controlled analgesia. Rarely is hospital admission essential for pain control, except for surgical blocks. Generally parents can be taught to provide pain medication.

The provision of adequate analgesia should not be confused with the intentional termination of life. Adequate pain control is essential for the quality of a child's last days of life. There is no evidence that adequate pain control shortens a child's life. Adequate attention and resources need to be directed to the humane and competent treatment of pain and suffering in all children.

Because most pain medications, especially narcotics, lead to constipation, the prevention of constipation is a requirement. This can be done by the concurrent administration of a laxative such as docusate calcium (dioctyl sodium sulfosuccinate; Colace), glycerin, or bisacodyl (Dulcolax) suppositories. All of these methods are used successfully with young children at home.

Nausea and vomiting. Nausea and vomiting can be more difficult to control than pain; however, these symptoms are less common. When they occur, they can cause substantial discomfort for children and families. Ondansetron hydrochloride, a serotonin-receptor blocker, is most effective.[11(p61)]

Sleeplessness. It is imperative for a child to sleep at night so that the parents also receive some rest. Drugs such as diphenhydramine hydrochloride (Benadryl), chloral hydrate, phenobarbital sodium, or diazepam (Valium) are effective.

First-aid measures. Families can be taught how to handle nosebleeds, seizures, diarrhea, and other predictable clinical problems. For stopping bleeding, either pressure or ice pack may be used over the bleeding area. The nose may be packed with an absorbable gelatin sponge (Gelfoam) or clean gauze. Most seizures can be controlled by administering medications such as phenytoin (Dilantin), phenobarbital, or diazepam. The patient's head should be turned to the side to keep the airway open. Efforts must be made to control all symptoms.

Parental anxiety. For parents who decide to use home-based hospice care, the anxieties associated with taking a terminally ill child home may be great. Most parents have not even considered the possibility of home care. Identified fears of families caring for a dying child include the unknown, abandonment by care providers, not being able to control symptoms, and thoughts associated with the child's dying at home.[12]

There is much about dying and death the family may not even consider, such as contacting a funeral home, whom they wish to notify of the death, how to tell the children at school, and effects on siblings. A hospice or home care nurse should gently counsel parents about these practical matters so they can be better prepared. At

this point of care, there should be no emergencies that require admission to a hospital. There is no longer any reason to call 911. If parents panic, they should be instructed to call a hospice or home care nurse. The coroner should be notified so that the death is not treated as a police case.

Unique Family Issues

Making Life More Meaningful Before Death and Bereavement

What is most important for this child and family? Some families celebrate an early Christmas or birthday. Other families need help with financial and other practical problems to be able to turn their attention to making the remaining time with their child meaningful. When a child dies, parents and siblings need those memories.

Reactions of Siblings

The ages of siblings and what they have been told and understand about the situation add great variability to response patterns and make generalizations difficult. Neglect and jealousy may be the most common. Siblings, especially younger ones, may feel neglected when attention is given to a dying child. They also may need reassurance that they are not responsible for the death of the child. Including siblings in helping to provide some of the care for the dying child may be useful, but the siblings need to be given time and space to acknowledge the difficulty of seeing their sibling so ill and the deterioration that occurs as death approaches. Removing a sibling from the home during the dying process should be avoided, if possible. Bringing in additional help may be more useful for all the family members. Children's concept of death is based on their developmental level and their own experiences. If a young child is removed from the situation, it may be more difficult for that child to understand and resolve the loss of a sibling. In a nine-year follow-up, most siblings said the experience matured them, and no more than one of five had long-term negative responses to the death of a sibling.[13]

What Is Death Like?

For parents caring for their dying child, uncertainty about what occurs at the moment of death is a major cause of fear. Most families have not witnessed a death, especially in their home. They do not have the clinical knowledge or experiences to know what to expect or even which questions to ask. Parents and other members want to ask but often do not even know how to ask. Therefore, physicians and nurses should speak to the specific details of the impending death, gently and sensitively taking into account the cultural background and level of knowledge of the family.

Symptoms that may occur during the actual time of dying and of death need to be described clearly. For example, 80% of a sample of children gradually and peacefully stopped breathing as they died.[14] The remaining 20% of children may have difficulty in breathing for the last few seconds or minutes, which is agonizing for parents to watch and extremely frightening for a conscious child. Dyspnea should be relieved with morphine. Propping the child up in bed can help relieve air hunger. Although erratic breathing (Cheyne-Stokes respirations) should be explained to the parents, no treatment needs to be given because the child is unconscious and therefore most likely not suffering. If there is rattle during breathing from increased secretions in the posterior pharynx, low-dose atropine sulfate can be given. Rarely will there be hemorrhaging. If there is any possibility for hemorrhage, the family needs to make the necessary preparations, such as having red washcloths or towels readily available.

Health care professionals should never abandon a dying patient. The telephone is an important tool in providing access to the families by the health care professionals they have learned to trust and who they depend on. A phone call can also allay the health care professionals' worries about the family members. Phone calls will be greatly appreciated.

A telephone is a key component in maintaining good symptom control. A nurse on a home visit can assess the situation and notify the child's physician, and medications can be ordered from the local pharmacy; in this manner, symptoms can be managed relatively easily.

"Do-not-resuscitate" orders for a dying child should be agreed on and understood by the family. Parents who have been prepared for the death may suddenly request resuscitation. At this critical time, resuscitation should not be done. The parents need to be gently reminded that resuscitation would only be prolonging dying and, in fact, would or could cause harm to their child. Parents may not be prepared for their emotional response to terminal symptoms. As noted earlier, many hospice agencies request that parents call their 24-hour line, not 911. The presence of a hospice team member can help parents appreciate the value of a peaceful passage at the time of death. The child needs to be respected. The parents should not feel guilty because cardiopulmonary resuscitation was withheld if they understand its futility in this context. The memory of a resuscitation attempt is usually a negative one.

Most parents will want to be present at the time of the death of their child. Holding and talking to the child during the last few minutes of their child's life can provide precious memories afterwards. To encourage the parents to tell their child at such a time that they love him or her seems so simple, but parents are not sure how to deal with a dying child. The death of a child is relatively rare in today's society. Encouraging a family then to spend some time with their dead child is important. Some parents may need time to acknowledge the death of their child, to let go and say good-bye.

There should be no need for a coroner's involvement in the expected death of a child at home. A physician or hospice or home care nurse should contact the coroner's office and inform them of the presence of a dying child in the home and provide the coroner with the name of the involved physician. A funeral home may be called when the family is ready for them to come. A few fam-

ilies may wish to take their child to the funeral home. This needs to be cleared, as some states do not allow a dead body to cross county lines. Some parents will wash and put clean clothes on their child. Allow for various activities as families will differ in what they wish to do.[15-18] It is important to be sensitive and supportive to what is meaningful to the family.

Bereavement Issues

Part of every physician's and nurse's responsibility is to give empathic support and guidance for bereavement. A health care team should be involved in careful planning before death. Referrals should be made if a physician or nurse is unable to meet the family's needs. Individual clergy, social workers, nurses, and physicians and such groups as Candlelighters, Compassionate Friends, and church members can help. Professional referrals are available for assistance from psychologists, psychiatric social workers, and nurses. Bereavement can be different for persons in the same family. Three styles of grieving were identified: "Getting over it," "Filling the emptiness," and "Keeping the connection."[19] Bereavement may take longer than anyone would expect. A common worry is of being insane with the feelings and emotions that a bereaved member may have.

Research done on bereavement concerned long-term parental bereavement patterns, persistent guilt, and ongoing grief.[8] The findings indicated that home hospice care for terminally ill children resulted in a more satisfactory resolution of parental grief on a long-term basis than death in a hospital.

Conclusion

Good communication by the health care team with the family is essential in the transitions from the goal of cure to palliation and finally to comfort. Dying children and their families need to be given the option of home care. Health care supports are necessary. Good symptom management, especially pain control, is feasible in the home. The dying process and care of the body following death need to be explained to the family. Relationships need to be established with local hospices. At the policy level, sufficient reimbursement needs to be established.

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Caring for Patients at the End of Life

How Ethics Consultation Can Help Resolve Dilemmas About Dying Patients

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Case Presentation

The patient, a 76-year-old woman with diabetes mellitus and high blood pressure, was treated for breast cancer with a left radical mastectomy 14 years ago and a right mastectomy 2 years ago. She received radiotherapy after both operations. A year ago, congestive heart failure developed for the first time, and she was discovered to have severe mitral stenosis and aortic insufficiency.

The patient underwent mitral valve replacement a month after surgical therapy but had a stormy postoperative course that included empyema, a chest tube placement, and later, sternal dehiscence. She was seen by several consultants, who disagreed about her clinical management. For example, plastic surgical repair of the sternal wound was suggested by one physician, but another thought this would be futile, as the patient's wound-healing ability seemed low. The proposed surgical repair would be major and would require an omental transplant into the wound after resection of a plate-sized area of necrotic tissue, sternum, and ribs.

The patient and her family, exhausted and discouraged, decided to go home and think about it. The patient's condition deteriorated, and during her first office visit two weeks later, she refused an operation or further hospital care. Although the patient's son and daughter-in-law urged her to reconsider and to accept surgical therapy, the patient declined and died at home six months after hospital discharge.

Discussion

This critically ill, elderly woman had multiple medical problems, including diabetes mellitus, hypertension, coronary artery disease, and valvular heart disease. One surgeon thought operative repair was indicated, but another thought the patient's overall condition made further surgical intervention futile. The patient initially chose to have aggressive surgical treatment and then decided to forego further hospital care.

The case raises several difficult clinical-ethical issues, including making decisions about life-sustaining treatment, clinical disagreements among specialists, and the rights of patients to change their minds. This is the kind of case in which an ethics consultation might have been of practical clinical help.

Ethics consultation is a systematic, structured way to assist patients in reaching a personal, ethical decision and to help physicians guide patients and often their families by developing an ethically acceptable decision-making framework. It achieves these goals by exploring the patient's decision-making capacity and by considering the personal, social, and values issues of concern to the patient. It uses a variety of disciplines, including clinical medicine, health care law, clinical psychology, clinical economics, and moral philosophy and theology. These disciplines are applied to develop skills in ethical reasoning—skills that excellent clinicians in many fields of medicine learn and practice, especially when they serve as members or chairs of ethics committees and ethics consultation services.

Ethics consultation can improve the decision-making process and may reduce legal exposure for individuals and institutions, particularly for care given to patients near the end of life.[1] Indeed, the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) has recently approved standards for accreditation in ethics and patient rights that include institutional requirements for a functioning ethics process to resolve problems about life-sustaining treatment and resuscitation. Herein we discuss the current state of clinical ethics consultation and outline ways in which an ethics consultation might have helped this patient and her physicians arrive at an appropriate decision.

Emergence of Ethics Consultation

Hospital ethics consultations were first prominently discussed 11 years ago,[2] and soon after, the goals of ethics consultations were outlined.[3] Two investigators independently prospectively studied the use of ethics consultation services in teaching hospitals[4,5] and in a community hospital.[6] A prospective study of ethics con-

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sultation for children was done,[7] and outcomes standards for ethics consultation were proposed.[8]

Quality standards for ethics consultation were then proposed, as the functioning process and outcomes of consultation came to symbolize clinical and organizational ethics.[9] Some noted that it would be difficult to determine quality in the absence of goals and outcome measures.[10] Indeed, a procedural standard of care is emerging for ethics consultation, one that requires that ethics consultants assume professional responsibility, write notes in patients' medical records, and act as a patient advocate and clinical consultant.[11]

Identifying Issues for an Ethics Consultation

While the patient presented at the beginning of this article was still in the hospital, a primary care physician might have asked the ethics consultant to comment on some of the following questions:

- Given the disagreements between surgeons and given the acknowledged high medical risks of a wound repair procedure, how should we proceed? What should we recommend to the patient?
- Should the patient be apprised of the disagreements?
- Is the patient able to participate in making a decision?
- How can we help patients who change their minds in mid-course, initially accepting surgical intervention, but refusing treatment for postoperative complications?
- The family wants us to make a decision; what is their role in forming an appropriate treatment plan?

What is it about this range of questions that makes this a case for an ethics consultation instead of, say, a general medicine consultation or a psychiatric consultation? What does an ethics consultant do?

What Issues Require an Ethics Consultation?

An ethics consultation focuses on the wishes and choices of a patient. Of course, all good medical care should do so. But to an even greater degree than traditional consultants, ethics consultants are thoroughly patient-centered. In addition, ethics consultations usually address a range of issues that are associated with medical ethics, rather than, for example, psychiatry or general medicine. These issues include questions about the following:

- Foregoing life-sustaining treatment;
- Writing do-not-resuscitate orders;
- Evaluating advance directives;
- Assessing a patient's decision-making capacity;
- Balancing conflicting ethical and financial incentives.[12]

Where available from trained consultants, ethics consultations are accepted ways to resolve disagreements and conflicts that are not only technical disagreements but are also disagreements about patient values and choices. A study of 156 consecutive ethics consultations in community and university hospitals reported that requesting physicians were satisfied with the educational and patient management aspects of the consultation. Physicians found the consultation "very helpful" in identifying ethical issues, assisting with similar cases, improving the decision-making process, and helping the physician to make an ethical decision. Nearly all (97%) requesting physicians in both settings intended to request a consultation in the future.[6]

How Does Ethics Consultation Work?

Initially, an ethics consultant should talk with the requesting physician to uncover and clarify the ethical questions being asked. The questions mentioned earlier are typical, but other concerns, especially economic ones or those related to resource allocation, often underlie physicians' feelings of discomfort in recommending aggressive treatment with marginal benefits in an elderly patient as ill as the patient in this report. These concerns cut both ways—both in limiting care thought to be too expensive for its likely benefit (prevalent in capitated systems) and in prescribing tests and treatments to rule out even the smallest possibility of reversibility (prevalent in fee-for-service systems).

Before conducting the consultation, the consultant should seek permission, preferably from the patient if she retains decision-making capacity or, alternatively, from the patient's surrogate—in this case, her family. It is rare for a patient to refuse permission, but it does happen, and consent is an important beginning to an ethical process for ethics consultation.

The ethics consultant might begin by reviewing the hospital record, with attention to the present illness, hospital course, and written consultations from the various specialists. The patient should be interviewed to clarify her understanding of the situation, her goals, and her preferences for or against treatment. During this interview, the consultant should assess the patient's decision-making ability. Is her mental state normal, can she make reasoned judgments, and does she appear to understand her diagnosis and prognosis with or without medical and surgical treatment? What does she understand about the medical alternatives to surgical therapy?

After these data are gathered and with the assent of a competent patient, the ethics consultant should speak with other involved parties, including the patient's physicians, nursing staff, and social worker. These are persons who often can provide critical information about the patient's clinical condition and personal goals. Family members should be interviewed, particularly those who have had regular contact with the patient.

The ethics consultant can act as an additional information source to supplement and broaden the attending physician's perspective. It is the consultant's particular task to understand the patient's goals, values, choices, and reasons and to facilitate the interaction between the patient and her physicians. In the course of this understanding, the consultant may uncover additional clinical information that may be important in reaching a good decision.

Balancing Risky Behavior and Risk Management

Say, for example, that the consultant found that, just before her valve replacement, the patient had been bedridden at home and had been unable to concentrate enough to read or watch television. Despite her nonhealing chest wound, her cognitive function postoperatively may actually represent for her an improvement in her quality of life. The consultant could then explore her goals for continued treatment. What risks would she be willing to take to improve her functional status and quality of life? Does she want to live as long as possible? Why?

Older patients are often considerably more averse to risk than are younger ones.[13] Even young, healthy people, however, are commonly risk neutral or averse. Risk-averse behavior may indicate that a patient has successfully accommodated to a chronic painful or disabling condition that has reduced his or her functional status and quality of life.

By interviewing the patient herself, the consultant may discover that she is risk averse and would rather live for whatever short period she could outside the hospital than accept further surgical intervention. Alternatively, the consultant might find that, when all options were considered, the patient would be willing to take the chance of an operation to achieve a longer and more functional survival. The ethics consultant can best gather this vital information by speaking directly with the patient. A distant second-best approach is to speak with the family of a patient who has lost decision-making capacity about what they think the patient would prefer in these circumstances.

Treatments proposed near the end of life often force a patient to make a nearly faustian choice: live longer but not better. Many people hesitate to make any decision at all, or sometimes change their minds once or twice after reaching a decision.

Our point here is a simple one: do not assume. People are complex: some may adapt to new clinical circumstances by making new and unexpected choices. We cannot know without talking with a patient that she will certainly refuse an operation or, alternatively, that she will demand an operation because life is intolerable for her as a bedridden person. The ethics consultant labors to keep the patient and her goals and reasons at the center of the decision-making process.

Avoiding Iatrogenesis and Overtreatment

Consultants can sometimes help resolve cases by rediscovering the "case history." Here, the term "case history" refers not to the patient's medical history, but to the history of the physicians' efforts to treat the patient. Physicians often feel regret for past actions and inactions in a case and may feel legally exposed even when they are not. These feelings about earlier actions affect current decisions.

If a patient aspirates in a recovery room and suffers severe anoxic encephalopathy, for example, she will probably receive a much more prolonged course of treatment than if she had aspirated at home and was brought to the hospital in the same condition. Physicians often find it difficult to withdraw even futile treatment from patients when there are elements of iatrogenesis present. There is a professional urge to want to "fix" a situation that one may have caused. Although the urge is usually honorable, its results are costly for patients, families, the hospital, and the health care system.

In the case presented here, the general surgeon undoubtedly felt bad about the patient's postoperative complications, even though they may have been anticipated. When the procedure being contemplated is a high-risk, last-ditch effort, factors like physician regret, the risk of a negligence claim, the past relationship with the patient, and the likelihood of clinical failure may be important in the physician's dynamic in recommending an aggressive approach.

Sometimes the process of consultation, if done with sufficient sensitivity, can acknowledge the intensive, well-intended effort a conscientious physician has made. It is the ethos of physicians to blame themselves, to overcompensate, and to try to fix what is broken, irrespective of whether they are at fault or whether the problem can be fixed. This all-or-nothing approach is appropriate if it is a patient's goal, if she understands the medical risks and benefits of pursuing it, and, some would insist, if it is fair to others who have a claim on those medical resources. Subordinating one's own feelings to permit the patient to reach the decision that is right for her is a respectful, personal act.

Physicians seem to make different decisions for elderly patients than for younger patients with the same illnesses. Exploring how many physicians reach sound ethical decisions and whether the usual decision-making process may be modified in this case by an obvious fact, the patient's advanced age, allows the identification of the framework for clinical-ethical decision making.

Making Clinical-Ethical Decisions

Physicians usually make decisions based on considerations of the four important elements of a case[14,15]: medical indications, patient preferences, quality-of-life factors, and contextual factors. The ethics consultant can use this clinical framework with colleagues, trainees, and students to help structure and analyze the issues in a case.

Medical indications involve establishing a diagnosis, formulating a treatment plan, ascertaining the prognosis, and tailoring recommendations to the specific needs of the particular patient. *Patient preferences* are the wishes of the patient based on her own values, attitudes, and goals. *Quality of life* is a judgment by a third party (often the family or the physician), incorporating as much information as possible from the patient, about whether a patient's life is worth living and, therefore, whether the patient should be given the particular treatment under review. *Contextual factors* are aspects of a case that constitute a benefit or burden to a party other than the patient, including the wishes of the family, the allocation

of scarce medical resources, the economic costs to society, and the opportunities for medical research.

In most medical encounters, the first two components, medical indications and patient preferences, determine the decision. When they come into conflict, the competent adult's preferences usually prevail over medical indications. In the past, neither quality-of-life considerations nor contextual factors carried much weight in the decision-making process. When the medical indications are unclear and the patient's preferences unknown or unknowable, these other factors become more important.

Of course, in our changing health care system that emphasizes cost containment, these contextual issues are used increasingly to guide decisions. In some cases, ethics consultants can help to clarify financial constraints and identify financial conflicts of interests.[16-18]

This special way of thinking about cases and the clinical approach to ethics consultation take an involved, patient-centered view of what needs to be done.[1] Other approaches describe ethics consultation differently. One author sees family therapy as the most reasonable approach and locates the foundation of ethics consultation in psychotherapy.[19] Others see ethics consultation as mediation and use alternative dispute resolution to attempt to reach agreement between disagreeing parties.[20] Some think ethics consultation should be viewed as a quasilegal process and an ethics committee as a quasijury.[21]

Each of these other approaches has philosophical merit. Yet, none of them insists on two clinical goals for the work: assisting patients in reaching a personal, clinical decision and helping physicians to develop an ethically acceptable way of identifying and clarifying ethical issues and making decisions to guide patients and often their families. These goals, with the patient's values in mind, make the clinical approach to ethics consultation one that many physicians and patients find familiar and comfortable.

Caring for Older Patients

In the care of some older patients, such as in the case presented here, the order of the decision-making structure may be inverted for several possible reasons. First, the medical indications may be unclear because of the complexity of the current illness and needed medical judgment. Second, a patient's preferences may be overridden because they are not elicited, because they are elicited but discounted in favor of family preferences, or because the patient's decision-making capacity may be questioned. Third, quality-of-life and contextual factors may play an important role: age per se is often automatically judged as a negative quality of life, and cost of care is often measured in expected months to the end of life, without regard to medical factors.

The complexity of an elderly person's medical problems may muddle the traditional decision-making strategy of physicians, to the possible disadvantage of a patient.[22] In the case presented here, physician disagreement even at the level of medical indications created major difficulty in the decision-making process; when a second opinion conflicted with the first, it was difficult to arrive at an appropriate plan of action and a clear recommendation to the patient, and an ethical dilemma ensued.

As this case suggests, there may be a tendency to give insufficient attention to an elderly patient's preferences. Physicians tend to talk to families rather than to the patient about what an elderly patient might want. Because elderly patients may become temporarily disoriented in response to acute illnesses, they should be asked their preferences before they become ill, preferably before they are admitted to a hospital.

Second Opinions, the Refusal of Surgical Treatment, and Documentation

In a recent study of a second-opinion program for coronary artery bypass graft operations, it was found that, given two conflicting opinions, patients often choose a nonsurgical option.[23] The likelihood of a patient accepting one opinion over another depends in part on how knowledgeable, concerned, and persuasive each of the disagreeing physicians appears to be in the view of the patient and family.[24]

Not long ago, physicians, acting alone, paternalistically, and beneficently, would have made the final decision themselves. But in the past quarter century, we have reached agreement in this country that patients have the right not only to participate in these decisions, but to make their own decisions. Ultimately, most patients are willing to discuss the risks they are willing to take and to consider the differing functional outcomes, expected survival rates, and financial ramifications provided by alternative courses of action. In a manner often surprising to many physicians, patients want to talk about these difficult issues.

When clearly documented in the record, such a conversation can serve many purposes. It engages the patient in forming a therapeutic partnership with a physician or team of physicians as work proceeds to develop a treatment plan. It allows the patient to express values and permits the physician to understand the patient's choice. Equally important, the patient's reasons for her choices can be understood, and disagreements can be discussed. Goals for treatment can be agreed on. Making the components of decision making open and clear and documenting patient choice clearly and in detail in the medical record are also part of malpractice prevention and risk management. Such documentation is every risk manager's dream and can and should be a part of every ethics consultation.

This Case

In the case presented here, the ethics consultation might recommend that the physician greatly value the patient's verbal advance directive to limit hospital care, even over the family's urging. The best way to conduct this discussion is to include the patient and family in another office visit to consider not the risks and benefits, but rather, the patient's reasons for avoiding surgical

treatment and reentry into the hospital. Rediscussing risks and benefits may have the effect of browbeating the patient, which should be avoided. The consultant could offer to assist the surgeon in speaking with the patient, if the surgeon wishes, and the consultant could also suggest a family meeting. In this way, we can learn more about the woman's comfort and how she might gain it.

Excellent documentation of this office visit is important to prevent any future charges of negligence by family members. After reaffirming her preferences, the surgeon should attempt to win over family objections. Focusing on the patient's own choices is the best strategy.

Conclusion

For clinicians, an ethics consultation can improve decision making, show staff how to identify and resolve ethical issues in a dying patient, clarify applicable law, and help achieve an ethical outcome in the case. For the institution, consultation can reduce liability exposure, complement risk management and quality improvement, and help to meet JCAHO accreditation requirements in organizational ethics and patient rights. For patients, consultation can improve communication between the patient and her physicians and between the patient and her family, especially when advance directives are unclear or uncertain, when adequate pain relief and proper care near the end of life are in question, and when decision-making capacity may be impaired or absent.

Basic clinical ethics is a tool for decision making that every clinician should learn to use. Yet, as in other clinical fields in which physicians may be grounded but not expert, well-intended physicians may find it difficult to use the skills and play the roles of an ethics consultant. To identify ethical issues and help to resolve especially difficult patient care problems, ethics consultation should be available to patients and clinicians as part of high-quality, cost-effective, compassionate care.

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Caring for Patients at the End of Life

Clinical Management of Dying Patients

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Dying is universal, and death should be a peaceful time. Myriad comfort measures are available in the last weeks before life ends. Discussions about end-of-life issues often suffer from lack of informed opinion. Palliative care experts have identified specific somatic and psychological sources of distress for dying patients and their loved ones. Pain, shortness of breath, nausea and vomiting, and fear of abandonment contribute substantially to both physical and psychological discomfort toward the end of life. Simple, effective methods exist for relieving those symptoms. Knowledge about the natural events associated with dying and an informed approach to medical and psychological interventions contribute to systematic and successful comfort care. We describe the origin of physical and psychological distress at the end of life and provide strategies for alleviating many of the discomforts.

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Death is our common destiny.[1]

Medicine encompasses more than saving lives. Assuring a patient's comfort and dignity at the time of death should be a natural part of the patient-doctor relationship. Many physicians receive inadequate training in how to manage the dying process, and many enter into such situations with limited confidence. Patient and family expectations may complicate this dilemma. Some see physicians as gatekeepers to comfort care at the end of life, but others think that they focus only on rescue from disease. They fear that medical technoogy, relentless in its obsession to cure, will extend disease into prolonged dying, perpetuate intractable pain, and strip the patient of dignity.

Such concerns are rampant, and in the past decade they have generated substantial public controversy. Debate on issues surrounding dying often stems from lack of knowledge about principles of management and available resources. The care of dying patients gets little time during medical education, and it is a scientifically neglected area that badly needs more research.* Nevertheless, contributions from palliative care specialists, hospice workers, and others have produced a substantial body of clinical knowledge and demonstrated that skilled, compassionate care can assure a comfortable and dignified death in most cases. In this article we briefly review the major sources of somatic distress in dying persons, describe the psychological needs of patients facing death, and discuss how physicians can adopt an organized and supportive approach to patient care when cure or extending life is no longer an appropriate goal.

*See N. MacDonald, MD, "Suffering and Dying in Cancer Patients—Research Frontiers in Controlling Confusion, Cachexia, and Dyspnea" on pages 278-286 of this issue.

The Dying Process

When does dying begin? For patients with slowly progressing lethal disease, it begins in a psychological sense at the time of diagnosis. For others, dying emerges suddenly in the wake of a catastrophic event. For those with a prolonged course at the end of life, death often follows a cascade of crises. Still other patients undergo enormously distressing cycles of treatment, remission, and the return of disease. The trajectory of the dying process, in part, determines patient and family needs when the end approaches. It also determines the needs that patients and families will have for information and the extent to which family members and friends can be recruited into care-providing roles.

Psychological and biologic markers signal the progression to death. Cognitive function in many terminally ill patients diminishes markedly in the weeks before death, and restlessness, air hunger, pain, and delirium are common in the last 48 hours.[2-4] Specific observable changes signal when death is imminent, usually in the days preceding the final event. Not every dying patient goes through all the changes, but knowledge that these are normal human patterns gives solace to patients, family, and friends, while guiding caretakers in providing comfort care (Table 1).[5]

Sources of Somatic Distress for Dying Patients

Articles in the medical literature indicate that unrelieved pain, shortness of breath, and nausea or vomiting are among the most common causes of somatic distress in the days, weeks, and months preceding death.[3,4,6-13] Physicians predicting the death of patients in their care should prepare to deal with these problems before they emerge.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
NSAIDs = nonsteroidal anti-inflammatory drugs

Other noteworthy problems include confusion, restlessness, itch, disturbed bladder and bowel function, disrupted sleep, low energy, sedation, and cachexia. The last of these is often a greater source of distress to families and caretakers than to patients and is probably a natural part of preparing to die.[14] Cachexia has great practical importance because it depletes a person's energy, marks malnutrition and decline, and interferes with the ability to socialize at meal times[15]; it is particularly refractory to treatment. Rarely does any one symptom occur in isolation. The clinical challenge is to treat all discomforts without compromising the dying person's mobility or cognitive function. We discuss in detail the major somatic problems of pain, nausea and vomiting, and dyspnea.

Pain

Pain is the symptom dying patients fear the most, and although far from ubiquitous, it is a common problem in many terminal illnesses, including cancer and the acquired immunodeficiency syndrome (AIDS). Often pain is a marker of disease progression, but it can also emerge as a toxic effect of treatment or as an exacerbation of preexisting or coexisting conditions.[16] Pain interferes with activity, impedes the enjoyment of even simple satisfaction in daily living, and can prevent important and nurturing social exchanges near the end of life. It is a frequent cause of psychiatric symptoms in patients with advanced cancer. Indeed, when pain and a psychiatric disorder such as severe depression coexist, controlling the pain should be the first objective.[17]

Pain in terminally ill patients fits into two broad categories, nociceptive and neuropathic. Nociceptive pain—normal neural activity mediated by healthy intact nerves—signals tissue trauma, inflammation, or both. It can be either somatic or visceral in origin, the latter manifesting as diffuse, poorly localized distress or sometimes in patterns referred in characteristic ways to the body surface.[18] Neuropathic pain results from damage or entrapment of nerves caused by disease progression, surgical therapy, irradiation, or chemotherapy. In some patients, pain results from central lesions such as damage to the ventral or medial thalamus. Neuropathic pain has peculiar qualities that sometimes resist conventional approaches to pain control.

TABLE 1.—*Signs That Death Is Near (Within a Few Days)**

Hypersomnolence
Disorientation
Irregular breathing
Excessive secretions
Visual and auditory hallucinations
Decreased clarity of sight
Decreased urine production
Mottled skin
Cool extremities
Truncal warmth

*Adapted from Hospice and Home Care of Snohomish County, Washington State.[5]

The most common source of nociceptive somatic pain in patients with cancer is metastasis to bone. The primary causes of pain in metastatic disease are inflammation of the periosteum and increased intraosteal pressure from tumor infiltration.[18,19] Not all of the sites that appear on a bone scan hurt; over time, a specific lesion may flare up or quiet down in unpredictable ways.[20] In some cases, bone lesions can cause fracture and acutely painful crises such as vertebral collapse. Most patients derive sufficient benefit from parenteral analgesics, but palliative irradiation of focal lesions can alleviate intransigent pain and prevent catastrophic fracture.

Visceral pain may indicate direct tumor infiltration, swelling, distension of ducts, or obstruction within organs. Inflammation can cause or exacerbate it. Because pain often elicits autonomic reflexes, visceral pain can contribute to nausea, affect bowel and bladder function, and alter appetite. When referred to the body surface, visceral pain can cause skin sensitivity in the area of referred pain and sometimes provoke muscle contracture or spasm in the affected area, thus creating more pain.[18]

Neuropathic pain syndromes include plexopathies, peripheral neuropathies, and central pain states. Pancoast's syndrome (a superior pulmonary sulcus tumor), for example, is a brachial plexopathy that causes lancinating deafferentation pain in the affected shoulder and arm.[18] Neuropathic pain differs in character from somatic pain in that it tends to occur after a delay following a causative event (for example, delayed response to pinprick), its qualities are dysesthetic (burning, "pins and needles," "electricity-like," and sometimes paroxysmal), and its somatic reference tends to follow patterns of sensory loss. Peripheral nerve injury sometimes involves exquisite tissue hypersensitivity in the absence of inflammation; patients complain that light touch and minor temperature changes cause or exacerbate pain (allodynia).

Nausea and Vomiting

Nausea and vomiting are frequent, often severe sources of distress for patients with life-threatening illness.[21] Sometimes these symptoms are iatrogenic; in other cases, they occur because of visceral lesions. They are common during cancer therapy and during the course of AIDS,[22,23] but can emerge with the use of palliative medications. Disease in a variety of organs, including the brain, may cause these symptoms. Nausea interferes with a patient's ability to move about and interact socially; it is a side effect that often limits the dosage of opioid drugs to the level of full pain relief. Vomiting, which does not always accompany nausea, is particularly dangerous because it may promote dehydration, electrolyte imbalance, aspiration pneumonia, and malnutrition. As a social event, recurrent vomiting is disastrous. Patients who need the comfort of friends refuse social contact, and family members agonize over the problem.

The mechanism and mediators of nausea and vomiting are complex and remain incompletely defined. Both central and peripheral factors play a role. The chemoreceptor trigger zone and the nucleus solitarius are located in a highly vascular area of the brain stem devoid of an effective blood-brain barrier. It is rich with opioid, dopaminergic, cholinergic, histaminergic, and serotonergic receptors. Investigators hypothesize that activation of these receptors stimulates an emetic center that, in turn, produces nausea and can initiate vomiting. A vestibular component is particularly prevalent with opioid-induced nausea and can severely limit ambulation. Impaired gastrointestinal motility, associated with diabetes mellitus, chemotherapy-induced autonomic neuropathies, opioid therapy, inactivity, and primary gastrointestinal disease, is an important cause of nausea or emesis.[24-26]

Dyspnea and Cough

Shortness of breath or dyspnea is the sense that breathing is difficult, causing a person to increase ventilation or reduce activity. It is not necessarily related to exertion.[27] Dyspnea is not synonymous with respiratory distress, which implies hypoventilation, hypoxemia, or both. Respiratory distress certainly is associated with, and a common cause of, the subjective feeling of breathlessness. Dyspnea can manifest as copious secretions, cough, chest pain, fatigue, and air hunger; its cause is complex and varied. Head and neck cancers can cause partial upper airway obstruction and often are associated with excessive secretions. Neuromuscular disease or generalized weakness will lead to restrictive airway disease with a secondary buildup of secretions that in turn can lead to obstructive lung disease. Cardiac failure can cause exertional dyspnea, tachypnea, orthopnea, paroxysmal nocturnal dyspnea, and cough. If left untreated, cardiac failure will cause pulmonary edema, which often imparts a sensation of drowning. Renal insufficiency can cause fluid overload and make cardiac failure more likely. Mediastinal disease, such as enlarged lymph nodes, can compromise both cardiac and pulmonary function, leading to dyspnea. Intra-abdominal disease—enlarging mass or ascites—will encroach on lung volumes and capacities, resulting in tachypnea to maintain minute ventilation, a common cause of subjective air hunger. Primary pulmonary disorders of many kinds can lead to dyspnea: chest wall, pleural, airway, or parenchymal tumor; infectious or aspiration pneumonitis; pulmonary embolus; bronchopleural fistula; irradiation- or chemotherapy-induced fibrosis; and chronic obstructive pulmonary disease.

Breathlessness can progress slowly over the course of a long illness, or it can present rapidly in association with acute decompensation and imminent death. It is a common feature in the last days of life.[28] Loved ones and clinicians often feel uncomfortable in the presence of a person who is short of breath.

Cough may or may not accompany dyspnea. It is often the symptom that brings a patient to medical attention and may have frightening connotations to patients and families, particularly if associated with hemoptysis. Heart failure can precipitate dry cough, but more commonly cough results from primary airway or lung disease, including pharyngeal irritation or restriction from tumor, large or small airway obstruction, reactive airway disease, mucous plugging, pleural effusion, and parenchymal disease.

Psychological Aspects of Care

Psychological factors are central considerations in the management of dying patients because the goals of care are to prevent or ease patient suffering. Careful attention to psychological aspects of the patient and family situation can help minimize family distress and bereavement. When psychological aspects of the dying process go smoothly, care providers also experience less stress.

Despite compelling reasons for emphasizing the psychological aspects of care when a patient is approaching death, some physicians ignore them. They distance themselves from the emotional needs of patients and families and continue to press on toward the unreachable goal of cure. Such behavior usually reflects insufficient training and experience in palliation. In this section, we briefly describe the psychological needs of dying patients, note the importance of family factors for the psychological aspects of care, and review several specific challenges that physicians often encounter in managing dying patients.

Needs of a Dying Patient

It is difficult to predict the psychological state and needs of a dying patient. Persons differ as a function of the trajectory of the dying process, across age cohorts, as a function of cultural background, and across levels of education and socioeconomic status. Nonetheless, certain psychological aspects of care recur frequently and merit comment.

The first is that a patient is unlikely to enter the process of dying and progress to death in a single mind set. Kübler-Ross contended that dying patients go through stages of denial, anger, bargaining, depression, and finally acceptance.[29] Her writings generated substantial controversy, but the fundamental point remains valid: the psychological needs of dying patients tend to change, and compassionate care requires that physicians tune into these changes and meet new needs as they arise.

Second, patients are vulnerable to specific fears. The most common is the fear of abandonment or dying alone in a medical technology environment separated from loved ones, that is, dying without warm human contact.[30,31] Patients often fear that they will be repulsive to others because of inadequate pain relief, poor control of bodily secretions, bad odor, and other socially offensive characteristics. It is important to protect them from the loss of self-image and feelings of isolation.

Smith and Maher found that certain attitudes can help people achieve a "healthy" death.[32] By questioning hospice coordinators, they identified the following issues of importance to people near their death:

- The presence of significant others (family, friends, or both);
- Physical expressions of caring—touching, hugging, kissing;
- A desire for the truth;
- Control in making decisions that affect care;
- Discussion of the practical issues of dying, such as finances and the family's future;
- An opportunity to review the past—pleasures, pains, accomplishments, and regrets;
- Personal appearance, cleanliness, and social presentability; and
- Religion and spirituality (independent of the patient's involvement in organized religion). Discussion of an afterlife was much less important.

Viewed collectively, these concerns suggest some important principles in the management of dying persons. Those for whom death goes smoothly are often persons who have a sense of control and involvement in decisions concerning care. They exercise opportunities to bring life to closure at a practical level, arranging their affairs and negotiating changes in family roles. They require truth and intellectual integrity rather than denial and evasion. Finally, "successful" patients are concerned about spiritual issues and the afterlife, but spiritual concerns do not equate with religiosity. This observation supports what hospice workers and chaplains have long known, that it is not necessary to be of the same religious faith as the patient to support that patient's spiritual needs.

Psychological Factors in the Family Setting

Because family members provide care, they can take important roles in the home setting—medication delivery, hygienic routines, monitoring of signs and symptoms—and they can provide organized and appropriate psychological support. Unfortunately, even healthy families may find it difficult to cope. For example, when the disease trajectory has involved many failed treatments, family members may be close to, or at, burnout. In some situations, patient and family feel that continuing survival causes everyone to suffer, and they believe collectively that death will resolve this. In such cases, it is generally best to draw on home hospice or other home care resources to take the burden off the family and to counsel them to consider the last weeks, days, or hours of a patient's life as an important time in the family history. In dysfunctional families, those with preexisting psychological problems, drug or alcohol abuse patterns, or poor family dynamics, it may require a physician advocate to protect the patient from an unnecessary conflict with a family member.[33] If certain family members tend to cause the patient stress and contribute to the suffering, it is important to direct their efforts away from the patient. Such problems are often subtle. For example, a well-meaning spouse, desperate to help and unable to accept the natural cachexia that the patient is experiencing, may insist on preparing elaborate meals, demanding that the patient eat. In this case, it is important to identify genuine needs that the patient has and direct the spouse's energy toward meeting them.[14]

American culture leads many people to think that dying is a horrible aspect of family life, a crisis only to be endured. Counseling can help patients and families understand that the end of life is an important time, for this is when patients take stock of what they have been, make important farewells to loved ones, provide final guidance and advice for family affairs, and engage in intense meaning making. Visiting the home and talking with family members can often be a valuable investment of time in the care of dying patients.

Psychological Challenges in the Care of Dying Patients

Perhaps the most difficult problem encountered is that of distinguishing normal psychological responses to crisis, such as anxiety and sadness, from psychopathologic responses, such as depression, panic disorder, and dementia. Unrelieved pain can produce psychiatric symptoms that will disappear when pain is controlled. Sometimes long-standing patient problems (such as alcoholism) create behavioral difficulties during the dying process. A patient's personality can also present challenges. Patients who have been neurotic all their lives will be so at the end of life and may pose particular difficulties in the family environment and in interactions with caregivers. When psychological problems appear to be pivotal factors in patients' and families' suffering, a mental health professional should be consulted.

It is also challenging to form an understanding of the needs and preferences of a dying patient and to fit the delivery of care to these needs. The fundamental rule here is that good care involves giving patients options. Patients' needs are sometimes shaped in unusual ways by cultural or religious factors. Needs may change as patients pass through different stages, so options must be reviewed and assessed periodically.

Providing information that fits patients' needs near the end of life can be difficult. Patients have both the right to know and the right not to know, if they are inclined toward denial and nonconfrontation with the truth. Physicians must be ready to adjust to changes in the desire for information. The one constant is that patients always welcome the assurance that their physician values personal comfort, personal control, and patient dignity.

Finally, to some degree physicians have to care for family members as well as patients. Most family members suffer psychologically during the dying of a loved one, but eventually they will go through the process of bereavement. Bereavement is a time of physical vulnerability, and bereaved persons are more likely to suffer impaired immune status and behavioral problems.[34-36] The physician should keep in mind, therefore, that helping a patient achieve a "healthy" death benefits the survivors as well and eases their bereavement and the attendant risks to health for the survivors.

Resources and Treatment Options

No one should die in physical discomfort or in psychological distress. Pain relief—with medications, nerve blocks, epidural catheters, and palliative irradiation or surgical therapy—skilled use of antiemetics, and careful titration of sedatives, psychotropics, or stimulants can abolish or control most distressing symptoms. At times patients' comfort must take precedence over possible side effects of intervention. The doctrine of double effect invokes the axiom that intervening on a patient's behalf may incur risks, including the possibility of hastening death. To prevent discomfort, some situations require deep sedation, with the accompanying risks of respiratory or cardiovascular collapse. Practitioners should define objectives of therapy precisely, explain all possible effects of treatment, and involve patients and families in decision making to the fullest possible extent. Psychological considerations go hand in hand with medical interventions. A multidisciplinary management strategy involving patients, families, physicians, nurses, psychotherapists, pharmacists, and clergy is optimal, if available.

Giving patients a choice is fundamental to good care. Physicians and patients should plan together to determine which problems are likely to occur, decide how they want to address those problems, and where the patient wants to die, so they may arrange for home health, nursing, or hospice services, as required.

Pain Management

Analgesic medications are the mainstay of pain therapy in dying patients. Both nonopioid and opioid medications are useful. Literature on the management of cancer pain is voluminous, having culminated recently in publication of the Agency for Health Care Policy and Research's *Clinical Practice Guideline: Management of Cancer Pain*.[37] The American Pain Society's *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* is a pocket-sized reference with recommendations and conversion tables for the use of analgesic drugs.[38] We refer readers to those resources for a complete discussion of pain-relieving modalities. We emphasize here that clinicians should treat constant pain with fixed, around-the-clock dosing schedules, while providing liberal medication for breakthrough or incident pain as needed.

Nonopioid analgesics. Nonopioid analgesics include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. All nonopioid analgesics have a ceiling effect, after which higher blood concentrations produce no increase in analgesia; they are antipyretic and do not produce tolerance. Effects are additive with the central effects of opioid analgesics. Therefore, for bone pain NSAIDs can be considered the first line of defense, with opioid medications added as needed to increase pain relief. Nonopioid analgesics are useful as a component of therapy for somatic pain, have less usefulness in the treatment of visceral pain, and usually offer little or no benefit for neuropathic pain.

TABLE 2.—*Classification of Nonsteroidal Anti-inflammatory Drugs*

Classification	*Drugs*
Salicylic acids	Aspirin, choline-magnesium trisalicylate, salsalate, diflunisal
Acetic acids	Indomethacin, sulindac, tolmetin, ketorolac tromethamine, diclofenac sodium
Propionic acids	Ibuprofen, ketoprofen, fenoprofen calcium, flurbiprofen, naproxen
Anthranilic acids	Meclofenamate sodium
Enolic acids	
Pyrazole	Phenylbutazone
Oxicam	Piroxicam

Acetaminophen is a direct analgesic of limited potency with no notable anti-inflammatory properties. Patients can use it in combination with any other analgesic. Hepatotoxicity is the most clinically important adverse effect of acute or chronic acetaminophen overdose, although nephrotoxicity can occur also,[39] as can thrombocytopenia (very rare). Acetaminophen is an excellent antipyretic. Most patients tolerate it without difficulty.

Nonsteroidal anti-inflammatory drugs have substantial anti-inflammatory properties; they inhibit cyclooxygenase and prevent the production of prostaglandins that sensitize nociceptors in peripheral tissues. Individual response to NSAIDs varies markedly and is idiosyncratic. Table 2 shows the various classes of NSAIDs. If a particular NSAID fails to provide relief after a reasonable trial at a standard dose (usually a week) or produces uncontrollable side effects, one from another class should be tried.

The most common NSAID toxicities are gastrointestinal disturbance and bleeding. Sucralfate, histamine H_2 blockers, the antisecretory drug omeprazole, and the prostaglandin analogue misoprostol, which has both cytoprotective and antisecretory activity, provide some protection against gastric and duodenal ulceration. Misoprostol may be the only agent that is effective in patients who do not discontinue NSAID therapy.[40,41] By inhibiting cyclooxygenase, which leads to decreased thromboxane A_2 levels, most NSAIDs, including aspirin, impair platelet aggregation. Exceptions include the nonacetylated salicylates choline-magnesium trisalicylate (Trilisate)[42,43] and salsalate (Disalcid).[44]

Opioid analgesics. Misunderstandings and myths about the safety and efficacy of strong opioid analgesic medications persist. These drugs are the cornerstone of almost all analgesic strategies in the care of dying patients, present little or no risk to life, and are simple to administer. Specific confusion exists with respect to respiratory effects of opioid medications and issues of drug tolerance, addiction, dependence, and abuse (Table 3).[45]

The term "opiate" refers to any compound derived from opium. Opioids possess morphinelike qualities and bind to one or more endogenous opioid receptor sites (μ, κ, or δ receptors). "Narcotic" denotes any compound that produces sleep.[46,47] We discourage using the term "narcotic" during patient and family counseling; it carries

TABLE 3.—*Opioid Tolerance, Dependence, Addiction, and Abuse*

Tolerance	A predictable laboratory and clinical phenomenon in which continued use of a drug leads to decreased efficacy (intensity or duration of effect or both)
Dependence	Physical dependence implies that cessation of a drug will lead to a withdrawal syndrome; psychological dependence is an emotional need for a drug either for its positive effects or to avoid the negative effects associated with abstinence
Drug addiction	A behavioral phenomenon wherein psychological and physical dependence on a drug lead to uncontrollable use and procurement
Drug abuse	Any use of drugs that causes physical, psychological, economic, legal, or social harm to the individual abuser or others affected by the drug abuser's behavior*

*From Rinaldi et al.[45]

more drug abuse than medicinal connotation in common parlance and evokes inappropriate concerns about drug craving and loss of personal control. Patients and families frightened by the term "narcotic" often feel comfortable with "opioid."

Pure opioid agonists such as morphine, hydromorphone, methadone, and fentanyl do not have ceiling effects. Patients vary considerably in analgesic requirement and pharmacokinetics; from time to time some persons need high doses for maximum pain relief. Physicians' concerns that such doses put the patient at risk for respiratory depression or reflect drug tolerance are common but misguided.[48,49] Setting an upper limit on opioid dosing for caution's sake is inconsistent with compassionate care and can cause needless suffering. Dosing should be limited only to maximize comfort when opioid side effects such as nausea emerge as major problems. When pain becomes severe, it is often best to dose to maximize pain relief and then decrease the dose to balance the analgesia-to-side effect ratio.[50-52] Opioids should never be withheld from patients with pain from life-threatening illnesses.

Opioids are not useful for all kinds of pain. At therapeutic doses they are effective for the dull, constant aching or sharp pains associated with somatic nociceptive processes. Opioids sometimes prove ineffective when given parenterally for pain of visceral origin, especially if the pain is intermittent. When delivered into the neuraxis by either the epidural or the subarachnoid route, however, opioids control visceral pain well, stimulating receptors at the spinal level to inhibit peripheral nociceptive input.

Controversy exists about the efficacy of opioids for neuropathic pain. Many clinicians avoid the use of opioid analgesics for pain from nerve injury, preferring the use of analgesic adjuvants such as tricyclic antidepressants, anticonvulsants, benzodiazepines, corticosteroids, and neuroleptic medications under the assumption that neuropathic pain is inherently resistant to opioids.[53] More recently, investigators have shown that such pains are not resistant to opioids, but merely less responsive and may require more drug.[52] A more scientific approach to neuropathic pain is to treat with an adjuvant drug, such as a tricyclic antidepressant, plus an opioid.[54]

Patients can take opioid analgesics by almost any route imaginable: oral, sublingual, parenteral, transcutaneous, rectal, neuraxial. The oral route is the first choice because it is inexpensive and dosing can be titrated easily.[55] The oral route may not be feasible in dying patients who suffer from gastrointestinal distress or dysfunction. In such cases, the parenteral route may be preferable. Most clinically useful opioids come in both oral and parenteral preparations. If intravenous access is difficult, opioids can be delivered subcutaneously by infusion or patient-controlled analgesia. A fentanyl transdermal patch (Duragesic) has been available for several years; with application every 72 hours, it can provide effective around-the-clock analgesia. Oral transmucosal fentanyl citrate has recently become available. Investigators have not yet established its use for dying patients, but early data suggest that it will be valuable in the treatment of breakthrough pain in patients who cannot swallow.[56]

We recommend that clinicians prescribe only pure opioid agonists for pain in a terminally ill patient. Of these, morphine sulfate is usually the least expensive and is available for delivery by multiple routes; oral preparations come in immediate- and sustained-release forms. Mixed agonist-antagonist or partial agonist medications, such as pentazocine, butorphanol tartrate, nalbuphine hydrochloride, and buprenorphine hydrochloride, can precipitate acute withdrawal in patients currently using morphine or another opioid, and they can block the benefits of pure opioids when additional drugs are needed for breakthrough pain.

The liver biotransforms most opioid compounds. It is important to note that even sick livers will continue that process and that the opioids have no intrinsic hepatotoxicity. The kidney and gut clear hepatic metabolites. In the presence of even mild degrees of renal failure, active metabolites may accumulate. Important examples are the metabolite morphine-6-glucuronide, which is a more potent analgesic than the parent drug, and normeperidine, a toxic by-product of *N*-demethylation of meperidine that can cause seizures, coma, and death. We do not recommend the use of meperidine hydrochloride for pain in chronically ill patients.

Nausea and Vomiting

Inexperienced clinicians tend to adopt a nonscientific, "shotgun" approach to administering antiemetics. Like pain, nausea responds best to around-the-clock, scheduled dosing of medications. Because several kinds of receptors stimulate the emetic center, it is sensible to employ a multidrug regimen, increasing drug doses until a positive response occurs or it causes unacceptable side effects.

Many antidopaminergic agents exist: metoclopramide hydrochloride, the butyrophenones droperidol and haloperidol, and the phenothiazines. Like NSAIDs, the effects of antidopaminergic drugs are difficult to predict and often idiosyncratic. If an agent does not work or causes undesirable side effects, switch to another within the

dopamine-blocking family. The butyrophenones and phenothiazines have a sedating effect that may be beneficial. Metoclopramide enhances gastric emptying, so it can be especially helpful in patients with decreased motility caused by disease or opioid drugs.

The histamine H_1 blockers diphenhydramine hydrochloride and hydroxyzine hydrochloride effectively inhibit the response at histamine receptors in the brain and will also counteract extrapyramidal effects that the antidopaminergic agents can cause.

The most clinically useful anticholinergic for nausea is scopolamine, available in a convenient transdermal delivery system. Single, multiple, or partial skin patches can be used, contingent on effects and side effects. A loading dose of 0.1 mg of scopolamine hydrobromide intravenously normally achieves rapid relief. Side effects are dry mouth and occasionally confusion. An alternative to scopolamine is the antihistamine dimenhydrinate; it has substantial anticholinergic activity, targeting cells in the vestibular nuclei.[57]

The serotonin-blocking agents, typified by ondansetron hydrochloride, are useful for chemotherapy-induced nausea and vomiting, especially in combination with other antiemetics,[58-60] and show some promise for the treatment of chronic nausea.

Nonspecific antiemetics include benzodiazepines, cannabinoids, the indirect-acting sympathomimetic ephedrine hydrochloride, and corticosteroids. Benzodiazepines bind to γ-aminobutyric acid receptors in the limbic system, which play no known direct role in nausea or emesis. Nevertheless, investigators have shown their use for anticipatory nausea in chemotherapy and nausea associated with anxiety, especially when used in combination with other antiemetics.[60-63] Cannabinoids also influence the limbic system and sometimes can relieve nausea refractory to other agents,[64,65] but they frequently cause cognitive and sedating side effects. Ephedrine is useful for motion sickness and nausea caused by hypotension. The mechanism by which corticosteroids work is undefined, but they also appear to be effective in combination with other antiemetics.[24,60,64,66,67]

Nonpharmacologic approaches to controlling nausea exist. Behavioral therapies for nausea and vomiting include hypnosis, cognitive behavioral training, progressive muscle relaxation, distraction, and reframing. To date, they have produced mixed results.[68-70] Behavioral methods appear useful for mild to moderate nausea but not severe problems. We recommend behavioral interventions for patients who have nausea or vomiting as an adjunct to medications, but not as a single therapy, and we note that these approaches require the patient to use a skill. When patients are approaching death, skill training is rarely appropriate. The literature suggests that acupuncture at the P6 point on the wrist may also provide relief to some patients.[71,72] This approach to nausea control merits further research.

Dyspnea and Cough

The treatment of dyspnea and cough in dying patients is similar to the general medical management of symptomatic patients without terminal disease. The objective is to treat the primary physiologic cause of the symptom to relieve the psychological distress and autonomic responses that accompany it. If the primary causes of dyspnea or cough are not treatable, then the use of sedatives and antitussives is paramount.

Bronchospastic disease may be due to infection, airway encroachment by tumor, or tobacco or other environmental causes. Bronchospasm may be reversible with the administration of β-agonists or anticholinergics by the systemic or the inhaled route, methylxanthines such as theophylline, corticosteroids, and the use of pulmonary toilet. If caused by infection, the appropriate antibiotic(s) should be used. Radiation treatment will often shrink tumors dramatically within a few days, providing considerable relief from dyspnea due to airway encroachment by mass lesions. Other cytotoxic regimens may also be appropriate, but the lag time before a beneficial effect tends to be long.

The treatment of heart failure will depend on the causes and should be tailored to the individual patient. Frequent follow-up and adjustment of medications are essential. Diuretics, inotropes, and vasodilators are the standards of therapy.

Dyspnea due to increased intra-abdominal pressure from ascites usually responds rapidly to paracentesis, although the reaccumulation of fluid is inevitable, requiring repeated drainage of fluid. Placing the patient in a comfortable sitting position is a simple and effective way to decompress intrathoracic organs.

Fluid retention from renal failure may respond to diuretics and careful fluid intake management, but refractory cases require dialysis. Clinicians should not consider the matter of renal dialysis lightly. It is invasive, cumbersome, expensive, and potentially dangerous. Patients and families should be active participants in the decision-making process. Renal dialysis may be lifesaving but may also degrade the quality of that life.

Neuromuscular disease that causes dyspnea is often troublesome to treat. Methylxanthines are the only agents available that may increase muscle strength, but the effects appear to be minimal.[73] When neuromuscular disease is severe and not reversible, mechanical ventilation is the only option. Again, the patient and the family must be active participants in the discussion, and clinicians must emphasize that mechanical ventilation almost always requires heavy sedation, which will degrade quality of life. Preliminary data in animals suggest that progestin or estradiol (or both) improve respiratory drive,[74] but these agents have no proven clinical value in humans.

Cough will often abate if it is the result of reversible upper airway, pulmonary, or cardiac disease. If due to excessive secretions from infection or chronic bronchitis, antibiotics may provide some relief. Irritation of the pharynx from chronic cough tends to perpetuate the symptom; it may be difficult to break the cycle. Anecdotal evidence suggests that a supersaturated solution of potassium iodide, three to five drops three times a day, is an effective pharyngeal lubricant. Often, sugar-coated

lozenges or candy and home remedies such as tea and honey are the best available interventions for cough due to pharyngeal irritation.

If dyspnea or cough does not respond to the above-noted interventions, then respiratory sedatives and antitussives will be necessary; opioids possess both properties. Opioids shift the carbon dioxide response curve to the right, attenuating ventilatory drive to hypercapnia. Therefore, a presumed mechanism of respiratory sedation is that patients are less aware or troubled by respiratory fatigue.[27] Alcohol, barbiturates, benzodiazepines, and phenothiazines also act as respiratory sedatives.[75] Although not yet studied formally, haloperidol is commonly used as a respiratory sedative.[76] Our clinical experience reinforces its efficacy in that role. In addition to any direct effects on the medullary respiratory center, all of these drugs reduce anxiety and cause central sedation. In addition, the opioids decrease oxygen consumption by decreasing myocardial work, left ventricular end-diastolic pressure, and systemic diastolic pressure.

Thick or copious secretions can cause severe discomfort for both patient and loved ones. The inability to handle secretions effectively compromises the ability to

TABLE 4.—*Treatment of Somatic Distress in Dying Patients*

Couse of Distress	*Comfort Core Modolities*	*Mechanism of Action*	*Major Side Effects*	*Relief of Side Effects*
Pain	Acetaminophen	Analgesic, antipyretic	None except with overdose	NA
	Aspirin and NSAIDs	Analgesic, antipyretic, anti-inflammatory	GI upset and ulceration; platelet dysfunction	Antacids, sucralfate, omeprazole, H_2 blockers, misoprostol
	Opioids	Analgesic	Nausea	Antiemetics
			Constipation	Laxatives, stool softeners
			Sedation	Reduce dose, stimulants
			Pruritus	Antihistamines, nalbuphine HCl, naloxone HCl
			Urinary retention	Reduce dose, catheterize, nalbuphine HCl (?), naloxone HCl
Nausea or emesis	Scopolamine	Anticholinergic	Dry mouth, confusion	Reduce dose or discontinue
	Dimenhydrinate	Anticholinergic, antihistamine	Confusion, dry mouth	Reduce dose or discontinue
	Diphenhydramine HCl	Antihistamine	Sedation, dry mouth, confusion	Reduce dose or discontinue
	Hydroxyzine HCl	Antihistamine	Sedation, dry mouth, confusion	Reduce dose or discontinue
	Ondansetron HCl	Antiserotonin	Headache	Analgesics, discontinue
	Haloperidol, droperidol	Antidopamine	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate (Cogentin), reduce dose, discontinue
	Phenothiazines	Antidopamine	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate, reduce dose, discontinue
	Metoclopramide HCl	Antidopamine, gastric emptying	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate, reduce dose, discontinue
	Benzodiazepines	Unknown effect on limbic system	Sedation, depression, confusion	Reduce dose, discontinue
	Cannabinoids	Unknown effect on limbic system	Sedation, confusion	Reduce dose, discontinue
	Corticosteroids	Unknown	Confusion, sleep disruption	Haloperidol may help
Dyspnea	β-Agonists	Bronchodilation	Tachycardia, restlessness	Sedative
	Anticholinergics	Bronchodilation	Tachycardia, dry mouth	
	Methylxanthines	Bronchodilation, (?) increased strength	Tachycardia, CNS signs with overdose	Decrease dose
	Opioids	Shift CO_2 response, sedation	As above	As above
	Benzodiazepines	Shift CO_2 response, anxiolysis, sedation	As above	As above
	Alcohol	Anxiolysis, sedation	Oversedation, confusion	Reduce dose, discontinue
	Barbiturates	Shift CO_2 response, anxiolysis, sedation	Oversedation, memory loss	Reduce dose, discontinue
Cough	Potassium iodide	Pharyngeal lubrication	Potassium toxicity	Discontinue drug
	Opioids	Antitussive	As above	As above

CNS = central nervous system, CO_2 = carbon dioxide, GI = gastrointestinal, HCl = hydrochloride, NA = not applicable, NSAIDs = nonsteroidal anti-inflammatory drugs

converse and often makes a horrible noise; in its extreme form, it manifests as the "death rattle." Drying agents such as scopolamine will help alleviate this problem.

Hemoptysis, or coughing up blood, is perhaps the most terrifying source of respiratory distress to patients and families. It is most common in lung cancer, affecting half or more of the patients at diagnosis[27] and about 25% of patients shortly before death.[77] Severe hemorrhage is a palliative care emergency,[78] requiring immediate intervention for the comfort of a patient and those around the patient. Death may occur within minutes. Patients, families, and practitioners should prepare for such an event. Signs of blood should be covered with bedding and towels, and a strong opioid plus a potent anxiolytic should be available to reduce the patient's awareness and fear.[27]

Conclusion

We have described the mechanisms of some of the most troublesome somatic symptoms that dying persons experience and have offered suggestions for treatment. Table 4 summarizes a sensible approach to managing those problems. At times, particularly when death is imminent, eliminating distress in an awake patient may be impossible. Comfort may require deep sedation and profound analgesia; death may come earlier as a result. This is not the same as euthanasia. The doctrine of double effect, which explains the relationship between the intended act (to provide comfort) and unintended consequence (the hastening of death), directs care providers to place the dying person's wishes first. It is essential, therefore, to clarify those wishes at the earliest possible time, to involve the dying person and loved ones in the decision process, and to state explicitly the intended results and the possible unintended consequences of treatment. We have suggested ways to assess psychological discomfort, recognizing that it is often due to somatic distress, and offer suggestions for successful intervention. Clinicians should emphasize autonomy and individuality when caring for dying patients. They should involve patients and families in all aspects of decision making when possible and nurture healthy attitudes toward the natural process of death. Heightened clinician and public awareness of available comfort care measures should promote rational debate about end-of-life issues.

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Caring for Patients at the End of Life

Suffering and Dying in Cancer Patients
Research Frontiers in Controlling Confusion, Cachexia, and Dyspnea

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Program directors acknowledge that critically ill patients, having few or no therapeutic alternatives, can have a negative impact on House Staff and students. They urged an exposure to outpatient oncology, where treatment successes are more frequently found.[1]

The above quotation is taken from an editorial that discusses the recruitment of medical oncology trainees. Some training directors apparently harbor the view that exposure to dying patients is not intellectually stimulating and may discourage their trainees. Whereas almost half of the rising number of cancer patients will die of their disease, until recently oncologists seemingly thought that only problems directly related to tumor biology, changes in the anatomic dimensions of tumors, patient survival, and treatment toxicity were deemed worthy of research interest.[2] Because physicians and the institutions in which they worked appeared to go only "so far" in addressing the needs of dying patients and their families, a default in care was perceived, which led directly to the formation of the palliative care movement. This movement is now established, albeit with a fragile base of support, in Canada and the United States, as well as in other parts of the English-speaking world, Europe, and in selected developing countries.

Although the vector of support for clinical cancer research has been directed elsewhere, my review of substantive advances in clinical cancer research over the past 15 years has highlighted the following:

- Managing cancer pain;
- Controlling nausea and vomiting associated with the use of chemotherapeutic drugs;
- Using adjuvant chemotherapy, radiation therapy, or both, in selected cancers;
- Introducing successful techniques for bone marrow transplantation; and
- Emphasizing quality-of-life studies in cancer clinical trials.[3]

Three of the five issues involve improvements in symptom control and concerns for patients' and families' social and emotional well-being. The simple observation that most opioids and other symptom-controlling drugs can be administered subcutaneously to patients who can no longer take oral medications has had an enormous benefit in the ability to discharge patients to their homes who would previously have required hospital-based intravenous or intramuscular parenteral therapy. Subcutaneous therapies can be readily administered in a home setting following patient and family education, with considerable implications for patients' well-being and reduced costs. Developments in the use of subcutaneous medication came about primarily without massive grant support, with much of the work being conducted in palliative care settings.[4-7]

Successful biomedical research usually requires a fusion of interest and involvement by basic scientists, clinicians, and funding groups. Although many controversies remain, the felicitous union of neurophysiologists and pharmacologists working in common effort with clinician-scientists changed our treatment of cancer pain. The fruits of their work have been appreciated and expanded by palliative care groups. Similarly, quality-of-life studies have been advanced by skilled research psychologists and psychometricians, working together with clinicians and nurses. The successful management of nausea and vomiting is an example of an excellent continuum of laboratory-bedside progress fueled by pharmaceutical industry support.

In this article, discussing symptoms common in patients with cancer and relevant to other disorders, I advance the concept that directed research on major symptom problems other than pain is worthwhile. This article will consider selected physical symptoms only, while recognizing that research on quality-of-life issues and on socioeconomic aspects of illness is also worthy of increased interest and support. Indeed, research on these themes is closely interrelated with symptom research. For example, the introduction of subcutaneous drug delivery systems influences quality of life and the socioeconomic balance between hospital and home care.

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Problems in the Conduct of Symptom Research

Palliative care research stands in contrast to the basic sciences, where investigations are conducted by workers able to control not only their experiments but also the environment in which they work.

Physicians or nurses in palliative care usually have a primary focus on patient care. They have little dedicated time for research and do not have ready access to established research or biostatistical support networks. Asking dying patients and their families to take part in a research program presents unique ethical issues. Once a trial is launched, changing patient conditions often prevent an investigator from controlling trial conditions and maintaining patients in a study.

Aside from these personal characteristics, there are myriad logistic and developmental factors that limit research progress in symptom control. These are listed in Table 1. A few of these factors will be selected for further comment.

The lack of academic recognition for the field of palliative care is a major impediment to symptom control research. In Canada, at present, there are 3 chairs in palliative medicine in the 16 Canadian universities and 8 recognized university divisions or groups. All of these programs are thinly staffed, and the chair recipients, who do not have the luxury of protected academic time, must fulfill their primary duties in patient care, education, and, increasingly, budget balancing and administration. I am not aware of any specific chairs in palliative medicine in the United States, and only a few prominent palliative care groups have academic status.

Can research initiatives in palliative medicine find a home in established oncology programs? Perhaps. But to date, as reflected in our publications, grant awards, and meeting presentations, the study of symptom control does not flourish. For example, in Table 2 is listed the distribution of articles in the 1994 *Journal of Clinical Oncology*

TABLE 1.—*Limiting Factors in Palliative Care Research**

Logistic—Democratic
Small population base—individual programs
Lack of training in research techniques
Balance of workload versus research opportunities
Problems in control of variables in rapidly changing patient populations
Academic priority
Lack of association with academic units
Where association exists, lower priority in comparison with oncology and other disciplines
Lower priority of granting agencies
Unrealistic expectations leading to excessive targeting and funding of certain fields, such as cancer chemotherapy trials
Developmental
Lack of internationally recognized classification and assessment systems
Absence of multi-institutional groups
Lack of tie-in of basic science and palliative care
Absence of support from large pharmaceutical firms
Semantics—What is palliative therapy?

*From MacDonald.[3]

TABLE 2.—*Classification of Articles in the* Journal of Clinical Oncology, *1994*

Subject	*Articles, No.*
Chemoimmunotherapy, phase II-III	32
Adverse effects, iatrogenic	18
Nausea and vomiting	6
Infections	6
Other	6
Symptom therapy	4*
Quality of life, psychosocial	4

*Two were reviews, and two were study articles.

on pharmaceutical or biologic attempts to alter the course of incurable cancers, where only modest progress has been made in advancing life expectancy. Their number far exceeds the paucity of studies on quality of life, social and emotional issues in cancer care, and symptom control in patients with advanced cancer. Iatrogenic symptoms, notably treatment-related nausea and vomiting, are frequently studied; tumor-induced symptoms are uncommonly considered in the oncologic literature.

Among developmental issues, in contrast to other fields of oncology wherein an established taxonomy provides the lingua franca for research design and comprehension, internationally recognized classification and assessment systems do not exist. For example, what are the specific dimensions of the cachexia-anorexia syndrome? Are there definable subsets of dyspnea that may lend themselves to different approaches?

In Canada, the public dollar is less available for research, and we are increasingly dependent on academic-industrial linkages. The interests of commercial firms must relate to the balance sheet. To date, few major firms have developed an interest in research aspects of symptom control in dying patients. Commercial interest in nutritional support for patients with the acquired immunodeficiency syndrome (AIDS) with cachexia-anorexia is an exception. This interest is cast more in a service than a research mode, however, as the argument for the use of total parenteral nutrition in these patients appears to rest on a narrow investigational base.[9]

A basic science-clinical continuum may not exist because we have failed to excite our basic science colleagues about the interaction between tumor biology and the production of symptoms. Why do some metastatic bone tumors, and not others, induce severe pain? Why are some adenocarcinomas, and not others, associated with profound cachexia and asthenia? Why is weakness a common complaint, even in patients who appear well nourished? Although correlations between molecular and cellular aspects of tumors and the aggressiveness of tumor growth and survival are increasingly available, similar correlations with the presence or absence of symptoms are not commonly found in the literature.

Relevance of Symptom Research

Clinical research aims to prevent or control illness, improve the quality of human life and experience, and

build a knowledge base for our current intellectual satisfaction and future research endeavors. It also informs policy makers, guiding them as they set priorities and implement public health programs in an increasingly complex milieu. A preeminent role should be assigned to problems of major import where research may lead to interventions that can be successfully introduced. In making their decisions, policy makers may consider the following factors[10]:

- The degree of benefit of a health care intervention;
- The odds of obtaining a benefit;
- The duration of beneficial intervention;
- The number of patients—and, indirectly, familial and societal members—who will benefit; and
- The cost of intervention.

Although many policy makers would regard this framework as a design for evaluating interventions aimed at prolonging life, the same guiding principles clearly apply to interventions that improve the care of dying patients. Using cancer pain as an example, we can apply these factors in the following way:

- *Degree of benefit*: Universal access to impeccable cancer pain management will substantially reduce the suffering of dying patients.
- *The odds of creating the benefit*: Cancer pain management, supervised by competent professionals with access to a range of drugs and relatively modest technical support, will improve the quality of life of more than 80% of patients with cancer pain.
- *Duration of benefit*: The trajectory of advanced cancer extends from a few months (patients with cancer of the pancreas and adenocarcinomas of unknown origins) to several years (cancer of the breast with predominantly metastatic spread to bone).
- *Number of patients*: 60,000 patients will die of cancer in Canada during 1995; the number of dying patients continues to increase.[11] About 70% of dying cancer patients have pain.
- *Cost of benefit*: The drugs required to manage cancer pain are not expensive. Specific therapeutic interventions with anticancer agents or technical procedures are more expensive, but palliative radiotherapy can often be administered in short courses. The role of cancer chemotherapy in producing a purely palliative effect, without prolonging life, remains to be defined.

The same framework can be applied to other major symptom complexes.

Ethical Issues in Studies at the End of Life

In a recent provocative article in *Palliative Medicine*,[12] a nurse-ethicist, Ms Louise De Raeve, argues that "strong moral grounds exist for objecting to research in the field of palliative care." She observes further,[12(p304)]

> [T]o research at all into the needs and experiences of this client group could be said to be an affront to the dignity of those people who are terminally ill, an expression of profound disrespect for the emotional and physical state of such patients.

There is no question that studies on dying patients present many complex ethical issues. Among others, the following issues stand out:

- Obtaining a truly informed consent is problematic in a group of patients in whom confusional states are common.[13]
- Adherence to a rigid protocol must yield to the exigencies of patient-family care.[8]
- Both the schedule and the invasive qualities of regular testing may add to suffering unless carefully planned and considered.

Nevertheless, contrary to De Raeve's view that research at the end of life represents exploitation by the living of the dying, I would argue that patients with advanced chronic illness must maintain the right to participate in a research program that may benefit themselves or others. To serve as a teacher for others, and to use one's suffering for the common good, is a powerful incentive for participating in research. Moreover, because studies on symptom control usually include as a primary objective the relief of a distressing symptom, a research patient may have an immediate opportunity to benefit from the fruits of successful research.

Forgoing research may create an ethical issue in its own right. Is it right to ignore promising leads and to allow patients to suffer who may benefit from the fruits of research? Are we paternalistic in so acting? Is it possible that the lack of research interest in the problems of this patient group within an academic center may translate into a general lack of interest and a withdrawal from care?

In balance, I strongly believe that the expansion of symptom-control research not only may help future recipients of the products of this research, but also, in a psychological and practical sense, may benefit the research patients who work with us in the clinical trials.

Symptom-Control Research as an Exercise in Prevention

Although we tend to think of the concept of "prevention" as primarily avoiding disease, early diagnosis of a problem, followed by successful intervention to prevent a future catastrophe, is a core concept in medical practice. For example, cancer control programs should consist of the following four balanced approaches:

- Preventing cancer through the elimination of environmental and behavioral causes.
- Diagnosing cancer early through the identification of precancerous conditions, or treating small, curable cancers immediately after malignant transformation.
- Treating to cure or prolong the lives of patients with invasive cancers (including rehabilitation).
- Preventing suffering through the impeccable management of symptoms associated with cancer.[14]

Chronic unrelenting pain results in changes in neurotransmission that lower pain thresholds and induce a crescendo effect.[15,16] It is possible that other symptoms, if not ameliorated when they first develop, may induce a

similar spiraling cascade that renders the symptom more resistant to treatment.

Although this point is perhaps self-evident, accepting the concept has major implications. It follows that our major initiatives in symptom-control research should be launched earlier in the course of illness, long before patients may be enrolled in a traditional hospice-palliative care program. For this to occur, the often artificial distinction between "active intervention" and "palliative care" must be erased. A corollary point: cancer centers must give higher priority to symptom-control studies.

Major Symptom Complexes of Patients With Cancer

The incidence of symptoms is partly dependent on the primary site of a tumor and its pattern of metastatic spread. Nevertheless, general surveys indicate that an individual patient may have as many as 23 symptoms at one time, whereas the mean number of symptom problems in a recently studied group in New York was 11.[17] Regardless of the tumor type, a subset of prominent symptoms of particular import, both because of incidence and the possibility of research-based improvement in management, can be identified. Currently the cachexia-anorexia syndrome with its component features of weight loss and asthenia, to the point where patients can no longer care for themselves, is the major symptom complex afflicting patients with advanced incurable cancer. Dyspnea is a frightful problem, associated as it is with fears of "choking to death." Dignity and freedom are both compromised when a confusional state develops in our patients, a common finding in the last days of life. A review of these symptom complexes can demonstrate both the intellectual challenge and the promise inherent in symptom research.

Confusional States

Impaired cognition and manifest delirium commonly occur in patients with advanced cancer.[18] The brain of a patient with advanced cancer is subject to many insults, including multiple drug effects, metastatic involvement, sepsis, and a plethora of metabolic abnormalities. After these factors have been excluded, for unknown reasons a substantive number of cancer patients will remain delirious. Is this due to iatrogenic causes we do not appreciate? Perhaps. William Osler, in his 1905 study of the dying process of 500 patients at Johns Hopkins University Hospital (Baltimore, Maryland), reported few cases we would interpret as examples of agitated delirium.[19]

Delirium robs patients of a dignified ending to life and causes anguish for both observing family members and health care professionals. The environmental, social, and pharmacologic management of delirious patients has been well outlined. Further studies on the judicious use of neuroleptic agents, both old and new, sometimes in combination with antianxiety drugs, may enhance our pharmacologic management.

An exciting new research initiative is based on the concept that the early diagnosis of cognitive impairment and the early implementation of corrective factors reduce the incidence of terminal delirium. In a recent study, Bruera and colleagues at the University of Alberta Faculty of Medicine (Edmonton) hypothesized that the early diagnosis of a confusional state, followed by adequate hydration and the rotation of opioids, may prevent mental deterioration.[20] Their concern about opioids is based on recent work that points out that active metabolites of these drugs may accumulate in cancer patients, particularly in the subset of patients who are dehydrated, with low plasma volumes and impaired renal excretion of metabolites.[21,22] Although this problem is most clearly characterized in patients receiving morphine sulfate, the same phenomenon appears to occur in patients being given hydromorphone hydrochloride.[23]

Since 1990, Bruera's group, using the Folstein Mini-Mental State Questionnaire, has monitored, on a twice-a-week basis, the cognitive state of patients on their palliative care ward.[20] Patients identified as cognitively impaired are adequately hydrated, their drug regimens reviewed, and if a patient is receiving an opioid, a switch to an alternate opioid is made. As a result of this practice, comparing patients admitted between 1988-1989 and 1991-1992, a higher number of patients thought to be cognitively impaired at the time of admission is noted in the 1991-1992 group. Subsequent agitated delirium substantially decreased between 1988-1989 and 1991-1992, however.

The study suggests that simple, inexpensive diagnostic and therapeutic procedures, implemented at the start of a confusional state, may abort the onset of a devastating end-stage event, agitated delirium.

Cachexia-Anorexia Syndrome

The cachexia-anorexia syndrome, with its component symptoms of loss of appetite, weight loss, and changes in autonomic function, with chronic nausea, constipation, and muscle weakness, is commonly encountered across the spectrum of chronic advanced illness. Any defining characteristics of this syndrome in cancer patients vis-à-vis patients with AIDS or advanced cardiovascular disease remain to be determined.[24] As stated in another forum,[25] until recently the cachexia-anorexia syndrome seemed to be accepted as an inevitable price associated with end-stage disease; we exhibited little curiosity about the syndrome's causative mechanisms or possible therapies, even though this symptom complex, more than any other, causes patients to be dependent on others, with consequent strain on family resources and the requirement for institutional care for prolonged periods before death.

From work often conducted in surgical metabolic laboratories and by groups concerned with sepsis, it was found that the cachexia-anorexia syndrome is probably induced by chemical factors produced as part of a host response or, on occasion, by similar factors produced by tumors.[26] A "chemical stew" bathes cancerous tissue with reactive host cells, the neovasculature, and tumor cells secreting molecules with unpredictable biologic effects. Whereas administering a number of cytokines, including

tumor necrosis factor, interleukins 1 and 6, and interferon gamma, produces abnormalities that closely mimic the cachexia-anorexia syndrome, it is likely that an interactive cascade involving multiple cytokines may be responsible for the syndrome in humans. Immune cytokines seem to be the prime causative suspects, but other tumor-produced factors also contribute to the cachexia-anorexia mosaic.[27]

If chemicals cause anorexia and weight loss, it may be possible to use specific inhibitors to control the syndrome. Antibodies to cytokines have been studied in animal cachectic states where they do attenuate the syndrome, but the effects of these agents in mediating human cachexia-anorexia remain to be studied.

Vigorous nutritional attempts, using enteral and parenteral solutions, have been been found wanting in tumor-induced cachexia-anorexia. Similar approaches are now in vogue in the management of AIDS-related cachexia, although research on their efficacy has lagged behind widespread clinical use.[9] Pharmaceutical interventions have generally not been successful.

Cyproheptadine hydrochloride. An important component of cachexia-anorexia is hypothesized to block serotonin-mediated inhibition of appetite in the hypothalamus. A recent controlled trial of cyproheptadine hydrochloride yielded inconsequential results.[28] Unfortunately, cachexia-anorexia does not appear to be mediated by hypothalamic pathways.

Hydrazine sulfate. Hydrazine, an inhibitor of gluconeogenesis, has been studied repeatedly both as an antitumor agent and as a treatment of appetite and weight loss. Uncontrolled studies seemed promising, but subsequent controlled studies of hydrazine sulfate by itself or together with chemotherapy have shown no benefit.[29,30]

Pentoxifylline. Pentoxifylline, an inhibitor of tumor necrosis factor, has been reported to be helpful in individual patients.[31] A recent clinical trial of five patients with AIDS-related cachexia showed no benefit,[32] but the results of a similar trial of five cancer patients were encouraging.[33] Pentoxifylline lowered elevated tumor necrosis factor levels in both trials, so this action may not correlate with the drug's effect on cachexia. Results of an ongoing randomized trial are awaited.

Corticosteroids. Corticosteroids have an appetite-stimulating effect, but the catabolic activity of these agents may balance any appetite-stimulating effect within a few weeks. Therefore, although they are useful short-term agents to improve appetite,[34] they probably do not lessen the cachexia-anorexia syndrome over time.

Androgens. Although androgens have been widely used as antitumor drugs in breast cancer, their effects on the cachexia-anorexia syndrome have not been well studied. Unlike most other adenocarcinomas, breast cancer does not usually elicit cachexia until the end of life. Asthenia independent of weight loss does develop in patients with breast cancer, however. Could androgens relieve or forestall this symptom? In the past, studies on androgen effects in breast cancer were directed toward changes in tumor state; whether androgens affect tumor asthenia is unknown, but studies of androgens in patients with hypogonadism and in elderly men suggest that they may favorably influence protein balance and a sense of well-being.[35]

Progestational agents. Progestational agents are currently the most useful drugs for alleviating some aspects of the cachexia-anorexia syndrome. Following reports that these agents produced substantial weight gain in women with breast cancer, a series of studies using megestrol acetate, a synthetic progestogen, demonstrated that in both AIDS and cancer, weight loss could be reversed and appetite improved, with few adverse effects.[36-38] Although the incidence of thrombotic disorders could theoretically be increased by the use of megestrol, the risk of arterial or venous thrombosis in a reported trial was no greater than in those receiving placebo.[39] The mechanism of action of the progestational agents is unknown.

The early enthusiasm for progestational agents, however, has been tempered following a few recent trials. Progesterone binds to P-glycoprotein and, in multidrug-resistant cell lines, may reverse this phenomenon.[40,41] Several clinical trials have studied the effects of megestrol acetate in patients with tumors that have had a modest response to chemotherapy and in whom there is a high propensity for the cachexia-anorexia syndrome to develop. Unfortunately, a recent trial on small-cell lung cancer did not show improvement in either quality of life or survival in patients receiving megestrol plus chemotherapy. An increase in thrombotic episodes and a nonsignificant decrease in survival in the group receiving megestrol was reported (K.M. Rowland Jr, MD; C.L. Loprinzi, MD; E.G. Shaw, MD; et al: "Randomized Double-Blind Placebo-Controlled Trial of Cisplatin and Etoposide Plus Megestrol Acetate/Placebo in Extensive Stage Small-Cell Lung Cancer: A North Central Cancer Treatment Group Study," unpublished data, July 1995). Another trial using megestrol in patients with advanced cancer who were not on chemotherapy concluded that those receiving megestrol had a shorter life expectancy.[42] In both of these trials, the dose of the progestational agent (800 mg per day) was higher than that normally recommended in clinical use (160 to 480 mg per day). Although the use of megestrol is, in my opinion, indicated in the management of the early stages of cancer cachexia-anorexia, it would appear advisable to keep doses in the lower range of efficacy and to abjure its use in patients with a history of thrombotic disorders or tumor-induced hypercoagulable state. Its use in combination with chemotherapy remains problematic; it may also enhance drug-induced neutropenia.[43]

Megestrol therapy appears to increase fat stores, but not to restore protein.[45] In short-term studies of a group of patients with restricted activity, it is not surprising that lean body mass is not increased. Key questions—does megestrol therapy improve muscular strength, relieve asthenia, and improve patients' functional state—are being addressed in current trials of megestrol, whose results should be reported over the next two years.

Gastrokinetic agents. In the mid-1980s, a group of investigators showed that patients with advanced cancer often have an autonomic insufficiency syndrome characterized by changes in blood pressure regulation, cardiac rhythm, and gastric atony. Administering metoclopramide hydrochloride, a prokinetic agent, has been shown to improve gastric emptying, with consequent improvement in appetite.[46] Other prokinetic agents may demonstrate similar benefits.

Dronabinol. The "munchies" are well known to be associated with marijuana use. Dronabinol, a synthetic form of Δ9-tetrahydrocannabinol, has been shown in a number of small studies to improve appetite in patients with cancer or AIDS.[47-49] Earlier studies using marijuana congeners as antinauseants showed that age and previous experience with marijuana influenced the outcome. Young patients experienced in using marijuana had reduced nausea and may have regarded any associated changes in mentation as a "side benefit" rather than a "side effect." Older patients did not share this interpretation.

Other agents. Many other drugs may influence the cachexia-anorexia syndrome. Currently included in this list are insulin, somatostatin, thalidomide, and cyclosporine. Further clinical trials are awaited.

Future Studies in Cachexia-Anorexia Syndrome

The foregoing drug list is not offered as a set of definitive recommendations on the current treatment of the cachexia-anorexia syndrome; these are contained in several recent review articles.[50,51] Rather, I cite evidence that various drugs can influence the syndrome to suggest that pharmacologic trials are promising avenues of research. Oncologists delight in "mixing and matching" drugs. To date, studies combining possibly useful agents, such as prokinetic drugs, progestational drugs, and (relevant to asthenia) stimulants such as methylphenidate, have not been reported. Borrowing from research in other fields, it may also be worthwhile to reopen studies on androgen. In keeping with the thesis that symptom management should be regarded as an exercise in prevention rather than as a reaction to established severe symptoms, pharmacologic trials should be introduced earlier in the course of illness than has been the case.

It may also be worthwhile to revisit the use of nutritional supplementation. Whereas the host of studies conducted in the late 1970s and early 1980s gave little reason to think that either enteral or parenteral alimentation would improve the lot of patients with advanced cancer and the cachexia-anorexia syndrome, these studies concentrated on biologic end points; we are not aware whether patients had a higher quality of life while receiving supplementary nutrition.

Today our surgical and infectious disease colleagues tell us that specific amino acids such as arginine and glutamine may have unique effects on protein balance, wound healing, and immune function.[52,53] Moreover, certain fatty acids, such as those found in fish oil (ω3-fatty acids) may influence cytokine production.[54] Studies of "designer" enteral nutrition, perhaps in combination with pharmacologic agents, that use patients' quality of life and maintained function as the critical end point are now worthy of consideration.

Research in cachexia-anorexia will continue to lag in the absence of a multidisciplinary supportive network. Descriptive terms and staging criteria for the syndrome require definition.[24] Oncologists and nutritional experts should be joined by other research colleagues, including experts in patients' functional assessment, muscle studies, health care economists, and family and patient representatives. Sponsorship of workshops to develop the necessary basic taxonomy and assessment format would be helpful. The formation of the "Nutritional Oncology-Adjuvant Therapy" study group has recently been announced.[55]

Dyspnea

Dyspnea is a common symptom in patients with advanced cancer, especially lung cancer, an increasingly common fatal tumor. In one report it was concluded that current approaches to the management of dyspnea, in contrast to that of pain, are inadequate. In a review of symptom management by an excellent London palliative care home care team, pain was well controlled throughout patients' final illness, whereas dyspnea scores did not improve.[56]

This evidence would suggest that, unless the cause of dyspnea can be reversed, patients must live with it, perhaps aided by sedation and simple physical comfort measures such as positioning, ventilation, and oxygen in those with hypoxia. Dyspnea is usually a multifactorial syndrome. Patients become conscious of a sense of respiratory distress as a result of signals from the respiratory integrative centers in the medulla. These centers receive stimuli from chemoreceptors (monitoring hypoxia and hypercapnia), receptors in the lung through the vagus nerve, and from the respiratory muscles. A stimulus to increase the rate and depth of breathing, a decrease in respiratory muscle strength, or a combination of both, may be interpreted as dyspnea. Based on these concepts, there are new ideas for alleviating dyspnea that are worthy of clinical trial support. These include research on opioids, respiratory stimulants, oxygen, and techniques to overcome muscle fatigue.

Role of opioids. Opioids have an established role in the management of dyspnea in cancer patients.[57] Similar to their effects on pain, these agents decrease patients' awareness of dyspnea. Opioids can also improve breathing efficiency and exercise endurance.[58,59] Whereas the effects of opioids are thought to be primarily mediated on the respiratory centers and the central nervous system, the presence of opioid receptors in the bronchial tree suggests that opioids may have local effects, providing a basis for studies on the use of nebulized opioids.

The conventional fear of depressing respiratory function in a group of medically compromised patients has probably limited the use of opioids to relieve dyspnea. This concern is probably overemphasized and should not block the use of regular low-dose opioids.[60,61] The risk of

respiratory compromise is diminished in patients who are receiving opioids for other reasons, as clinical experience suggests that tolerance to their respiratory effects develops over time.

Future promising research questions include the following:

- Is tolerance to the beneficial effects of opioids incomplete, and may opioid rotation be helpful?
- Are some opioids better than others for the relief of dyspnea?
- Is there a role for nebulized opioids? Perhaps fentanyl citrate, which is thought not to carry the same risk of inducing histamine release as morphine,[62] may be less likely to induce reflex bronchospasm in sensitive persons. Perhaps an active morphine metabolite, morphine-6-glucuronide, may be superior to morphine.[63]
- If permissive opioid-induced hypercapnia is effective in relieving dyspnea (some degree of permissive hypercapnia is now allowed in intensive care units), what levels of $Paco_2$ are safe and free of undesirable side effects?

Respiratory stimulants. The following drugs are worthy of study in combination with opioids:

- Phosphodiesterase inhibitors, starting with aminophylline and theophylline: in addition to central nervous system stimulatory effects, these drugs may improve respiration through their effects on respiratory muscles.[64]
- Progestational agents, which may have mild central stimulatory effects,[65] could also have helpful effects on respiratory muscle function (see earlier discussion on cachexia-anorexia).
- Methylphenidate, an agent that has been proved useful in balancing other central nervous system depressant effects of opioids,[66] may also have a stimulatory effect on the respiratory center. Stimulating the respiratory center, however, independent of an effect on respiratory musculature, may be the wrong way to treat dyspnea. Possibly a corollary discharge from the respiratory brain stem centers to the cortex will increase patients' sense of respiratory distress.

Oxygen. Oxygen is widely used in the management of dyspneic patients with hypoxia. But exercise performance in many patients with chronic obstructive pulmonary disease is not improved by oxygen use. As oxygen use is expensive, common, and cumbersome, finding the useful limits of oxygen therapy is an important research issue. Current views on the use of oxygen in palliative care have been well expressed.[57] It has been recommended that the "n-of-1" technique be used to identify patients who may benefit from oxygen therapy.[67]

External muscular support. Patients with advanced cancer tire readily. Those with the cachexia-anorexia syndrome lose somatic protein, which contributes to general patient fatigue. Vulnerable muscles include those with a high proportion of type II ("fast-twitch anaerobic") muscle fibers. The diaphragm and external accessory respiratory muscles (which contain 25% to 45% type II muscle fibers) of cachectic patients may therefore be particularly vulnerable to wasting, with subsequent fatigue.[68]

Many abnormalities contribute to the sensation of dyspnea, including changes in blood gas values, intrapulmonary pressure-stretch relationships, and the sensory input from fatigued, overworked muscles. Is it possible to mechanically assist these muscles to both improve respiration and diminish afferent muscle messages that contribute to the respiratory center's pattern that is interpreted as dyspnea?

Ventilatory support, usually in the form of continuous positive airway pressure, is commonly recommended for patients with degenerative neuromuscular disorders, failing respiratory muscles, and hypoxemic respiratory failure. In this situation, it appears to be useful only in patients who have dynamic hyperinflation—that is, they are breathing at a lung volume above their normal functional residual capacity because of the concomitant presence of some degree of airway obstruction. This scenario is certainly not universally transferable to patients with advanced cancer who have dyspnea. "Proportional assist ventilation," a technique matching the patient's unique respiratory pattern with ventilatory support, and negative-pressure ventilators (such as the "iron lung" used in the polio epidemic of the 1950s) are used in research studies involving patients with advanced chronic obstructive pulmonary disease.[69-71]

Dyspnea in cancer patients usually arises from multiple causes; failing respiratory muscle function probably contributes in most cases. Could intermittent ventilatory support relieve muscle load and cancer-associated dyspnea? Because of the relative ease of measuring both ventilatory values and patients' subjective dyspnea scores, the n-of-1 research design mentioned earlier could be used to select patients who would benefit from continued intermittent ventilatory support.

Conclusion

Several common themes run through this discussion of the research frontiers of important symptoms in cancer patients: A fusion of basic science and clinical interest is required to match the success achieved in the field of cancer pain. For both ethical and practical reasons, the recruitment to clinical trials of patients with early manifestations of these symptoms is essential. Patients with early symptom manifestations are found in the clinics of academic cancer centers and university hospitals, not in hospices. Symptom control research networks should include colleagues not ordinarily involved in clinical cancer research, such as health economists, neurologists, geriatricians, and respirologists. Support for research network development is necessary. An early task of these networks would be to refine symptom taxonomy and assessment techniques.

The current approach to symptom management espoused by colleagues in palliative care is exemplary and should be appreciated and applied by all physicians caring for patients with advanced cancer. There is reason to

think that we can build on this coda and improve our current approaches.

To cure sometimes; to relieve often; to comfort always.

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Caring for Patients at the End of Life

Medical Futility and Care of Dying Patients

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In this article, I address ethical concerns related to forgoing futile medical treatment in terminally ill and dying patients. Any discussion of medical futility should emphasize that health professionals and health care institutions have ethical responsibilities regarding medical futility. Among the topics I address are communicating with patients and families, resolving possible conflicts, and developing professional standards. Finally, I explore why acknowledging the futility of life-prolonging medical interventions can be so difficult for patients, families, and health professionals.

(Jecker NS: Medical futility and care of dying patients, *In* Caring for Patients at the End of Life [Special Issue]. West J Med 1995; 163:287-291)

With the development of new medical technologies during the latter half of this century, medicine has been able to keep terminally ill patients alive for longer periods of time without curing or ameliorating their underlying disease condition. The widespread use of artificial feeding and nutrition, ventilator support, cardiopulmonary resuscitation, and renal dialysis has meant that patients diagnosed with metastatic cancer, coronary artery disease, kidney failure, and other life-threatening conditions no longer regard their diagnoses as lethal. Yet, life-sustaining interventions have sometimes been a double-edged sword. Medical treatments that extend life may also result in patients spending their final days and weeks confused and debilitated, unable to breathe, eat, or urinate without the assistance of ventilators, feeding tubes, and catheters. Although patients live longer, they may find themselves confined to hospitals and intensive care units, where they are sedated and unable to interact meaningfully or to obtain comfort and support from the company of others.

Under what circumstances should providers cease life-prolonging efforts? When a patient reaches the final stages of a terminal condition such as AIDS [acquired immunodeficiency syndrome], should the patient be admitted to a hospital for pneumonia, receive intravenous infusions for fluid loss with diarrhea, or be prescribed antibiotics for a bladder infection? What about more invasive procedures, such as the insertion of endotracheal tubes, the use of defibrillators, or surgical repair of a bowel obstruction? When should providers attempt to prolong life, and when should their efforts instead focus on palliative measures?

In this article I address the general problem of forgoing the use of life-sustaining medical treatment in terminally ill and dying patients. I defend a patient-centered definition of medical futility, placing it in the context of end-of-life care. The ethical responsibilities of health professionals and health care institutions are discussed with regard to communication with patients and families, conflict resolution, and the development of professional standards about medical futility. In closing, I explore the reasons why acknowledging the futility of life-prolonging medical interventions can be so difficult for patients, families, and health professionals. Despite possible obstacles, refraining from medically futile interventions is often the best way to care humanely for patients at the end of life.

What Does Futility Mean?

At first glance it might seem that, if a patient's death is imminent, then the patient's entire situation is futile regardless of what physicians do. On the other hand, if a life-sustaining treatment is working, that is, keeping the patient alive, we may wonder how the question of futility can even arise.

To clarify these questions, it is helpful to note that the term "futile" refers to a specific medical intervention applied to a specific patient at a particular time. It does not refer to a situation generally or to medical treatment globally. Nor should "futile" be used to refer to a patient, or to care, as this may convey the impression that the patient is being abandoned or that comfort measures will no longer be undertaken.

Finally, futile treatments sometimes succeed in producing physiologic effects, yet provide no benefit to the patient. For example, cardiopulmonary resuscitation of a permanently unconscious patient may restore heart function, yet be regarded as futile because it does not confer any benefit that the patient can appreciate. Those who regard the goal of medicine to be helping the patient, not merely producing effects on organ systems or body parts, accept what is thus called a "patient-centered" definition of medical futility.[1]

A patient-centered understanding of medical futility involves attention to situations in which many effects can

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
AMA = American Medical Association

be produced on a person's body; only some will be appreciated as benefits, others will be perceived as harm, and still others will not be experienced by the patient at all. For instance, resuscitating a heart attack victim and returning her to full functioning is clearly a medical benefit. On the other hand, when an emergency medical crew is called to a nursing home to assist a patient who suddenly has dyspnea and ventricular arrhythmia, followed by cardiac arrest, and who is known to have widespread pancreatic cancer, the effect of attempted life prolongation may not be experienced as a benefit by the patient, but may instead be regarded as a detriment by adding to the patient's pain and discomfort at the end of life. In contrast to these situations, prolonging the life of someone in a persistent vegetative state through the use of a feeding tube is not experienced as either a burden or a benefit by the unconscious patient.

Futility may become apparent in the context of caring for dying patients in at least two distinct ways. First, a treatment may be quantitatively futile because the likelihood that it will benefit a patient falls well below a threshold considered minimal.[2] For example, it is futile for emergency workers to rush terminally ill patients to a hospital after a failed resuscitative effort in the field because there is virtually no chance that patients will survive and benefit from such efforts.[3,4] Second, a treatment may be qualitatively futile when the quality of benefit associated with an intervention falls well below a threshold considered minimal.[2] For instance, hemodialysis of a hospitalized patient dying of multiple organ system failure with no hope of survival to discharge is qualitatively futile.[5]

Some have objected to a patient-centered definition of medical futility, claiming that a treatment should be called futile only when it fails to produce any physical effect on the patient's body.[6,7] Supporters of a "physiologic" definition of futility argue that health professionals should avoid imposing their values on patients and families and that patient autonomy should be seen as inviolable.[8,9] Limiting health professionals' judgments about futility to the narrow, technical evaluation of whether a treatment can produce an effect may appear to rid futility judgments of any value dimension.

My response is that the goal of medicine is not merely to produce physical effects on patients' bodies, but to help patients.[10] Expressed differently, "the subject of medical care is the suffering patient, not a failing organ system."[1(p2197)] In contrast to a physiologic approach, which pictures the health professional's role to be narrow, technical, and even value free, a patient-centered view regards the provider's role as promoting patients' good by producing effects that patients can appreciate.

This stance is consistent with the historical and contemporary ethics of the profession. Since its earliest beginnings, medicine has focused on the ethical goal of helping suffering patients. The ancient Greek physician, Hippocrates, reportedly identified the purposes of medicine as twofold: first, "to do away with the sufferings of the sick" and "to lessen the violence of their disease"; and second, to recognize medicine's limits, "to refuse to treat those who are overmastered by their diseases, realizing that in such cases medicine is powerless."[11(p6)] Reflecting a continued commitment to these goals, the American Medical Association (AMA)[12,13] and many other medical organizations have affirmed medicine's inevitable limits.[14-18] According to the AMA's Council on Ethical and Judicial Affairs, physicians' obligation is to offer patients "medically sound" options, including interventions that can "cure or prevent a medical disorder" or "relieve distressing symptoms."[12(p2230)]

In addition to ignoring the ethics and goals of medicine, a physiologic approach overstates the value of autonomy, casting it as an ethical absolute. Although respect for the wishes of autonomous patients is clearly an important value, this value must be placed in context. Autonomy does not entitle patients to receive any treatment they want, nor does it obligate health professionals to provide interventions that are "countertherapeutic" or that are contrary to "role-related professional standards and conscientiously held personal beliefs."[19(p44)] Upholding autonomy as an ethical absolute belittles the importance of beneficence in medicine, by making the goal of benefiting patients a secondary, or even irrelevant, consideration. If the only task of medicine were to carry out patients' wishes, clinicians would be reduced to functioning merely as patients' instruments. By contrast, upholding standards of medical practice aimed at benefiting patients assigns importance to beneficence while preserving a role for patient autonomy.

Finally, defining medical futility in purely physiologic terms fails to deliver on the promise of offering a "value-free" role for the provider. A commitment to use all interventions that can produce some effect on a patient's body, unless a patient or surrogate explicitly refuses them, is hardly a value-free stance. Instead, it implies a strong commitment to biologic life; a commitment to medical technology for its own sake, rather than as a means of promoting patients' good; and a disavowal of providers' ethical responsibility to promote patients' good and to avoid harming them.

What Are Providers' Ethical Obligations?

Once disagreements about the meaning of medical futility are resolved, there remains the question, What are health professionals' ethical responsibilities? Should providers offer futile treatments to patients or surrogates? Should providers instead explain and discuss the situation more generally? Should providers attempt to exclude a discussion of futile interventions with patients or families altogether, with an eye to preventing possible conflicts from arising? If conflicts do arise over the use of a futile intervention, what constitutes a fair process of conflict resolution? May a physician unilaterally override a

patient or family? Or should physicians instead cede to patients' or families' wishes?

Where feasible, providers should communicate in advance with patients (or surrogates) about decisions to withhold or withdraw futile treatments. Sensitive communication serves many functions, including making providers accountable for their decisions, educating patients and families, building trust between providers and patients (or families), and averting concerns that resources are being rationed or that patients will be abandoned. Providers should use the occasion of discussing the withholding or withdrawal of futile treatment to affirm that everything possible will be done to support the patient at the end of life, including the aggressive use of palliative and comfort measures.

Although the ordinary obligation of health professionals is to refrain from offering or using futile treatments, in certain situations compassionate exceptions should be made. For example, a patient with widespread cancer whose death is imminent within a matter of hours or days may ask to be made a "full code" because the patient would like to live long enough to see a grandchild for the first time who is arriving from a distant state. Or a patient who will never leave the intensive care unit may want to stay on a ventilator long enough to provide emotional support to a grieving spouse who is in the process of slowly coming to terms with the patient's death. Agreeing to a time-limited trial may provide a patient or family an opportunity to come to terms with their situation and to gain a sense of control over their fate. These examples make evident that the appropriate steps for implementing general ethical guidelines to refrain from futile interventions vary from case to case.

In the event that a patient or family persistently requests a treatment that the health care team regards as futile, a process of sensitively negotiating the conflict should occur. Ideally, an institution's policy on withholding and withdrawing treatment will specify steps for resolving conflict. These steps may include, for instance, consulting with the institution's ethics committee or individual clinical ethics consultants[20]*; drawing on resources such as a chaplain or social worker to provide support to the patient or family; obtaining a second medical opinion; and facilitating further communication with the patient, family, or both. In most cases, pursuing a process of conflict resolution enables the patient, family, and health care team to reach agreement and bring the case to a point of closure. Even when the parties continue to disagree about what should be done, they may be willing to accept a compromise position. For example, if there is not a clear consensus in the medical community about the futility of a particular intervention for the patient, the medical team may agree to refer the patient elsewhere. Or if a treatment is clearly futile, the patient or family may agree in advance to discontinue treatment after a certain amount of time if there is no improvement in the patient's situation.

*See J. La Puma, MD, D. Schiedermayer, MD, and M. Siegler, MD, "How Ethics Consultation Can Help Resolve Dilemmas About Dying Patients," on pages 263-267 of this issue.

The final decision about whether or not a particular treatment is futile does not rest with any single person. Rather, the definition of medical futility must be grounded in general standards of care that are first articulated by the health care professions and then accepted by the broader society.[21,22] Guidelines about medical futility should be based on reliable empirical data about the effects of interventions on different patient groups, as well as careful ethical analysis concerning patients' benefit. Whereas debate about the meaning of futility and ethical implications continues, physician surveys show that physicians are already incorporating some concept of medical futility into decision making at the bedside.[23-25] Establishing general guidelines and standards that address medical futility is preferable to delegating decisions about medical futility to individual physicians at the bedside. Bedside decisions are often not thought through, not applied consistently, not accountable to the public, not decided democratically, and not insulated from arbitrary or invidious prejudice based on factors such as a patient's race or ethnic group. To minimize possible abuses, institutions should develop clear standards for withholding and withdrawing futile interventions. Such standards serve to educate and guide not only patients and families, but also health professionals and courts about the limits of medicine.[26]

Many institutions have already begun to incorporate the concept of futility explicitly into guidelines for the withholding and withdrawing of medical treatment. For example, Johns Hopkins Hospital (Baltimore, Maryland) has defined "futility" as any course of treatment that "is highly unlikely to have a beneficial outcome" or "is highly likely merely to preserve permanent unconsciousness or persistent vegetative state or require permanent hospitalization in an intensive care unit."[27] Local consensus is also developing in places like Denver, Colorado, where area hospitals jointly developed criteria for deciding that a treatment is futile.[28] Such guidelines establish, for example, that aggressive treatments, such as cardiopulmonary resuscitation, are futile and should not be provided for patients who are bedfast with metastatic cancer, patients with AIDS who have had two or more episodes of *Pneumocystis carinii* pneumonia, or patients with multiple organ system failure with no improvement after three days of intensive care.

What Makes Acknowledging Futility So Hard?

Despite the importance of emphasizing patient benefit in the care of dying patients, health professionals often feel compelled to continue with nonbeneficial interventions. Interviews with physicians and nurses found that almost half (47%) of all respondents reported acting contrary to conscience in providing care to the terminally ill, with four times as many providing overly burdensome treatment than undertreatment.[29] Especially if a patient or family member requests that "everything possible" be done, the health care team may be reluctant to go against the patient's or surrogate's wishes. Unbalanced respect

for patient autonomy, well-meaning compassion for grieving family members, fear of legal liability, and avoidance of death are among the factors that can contribute to the use of futile treatments at the end of life.

Setting aside legal concerns and economic self-interest, what leads health care providers to prolong patients' suffering by futile attempts to beat the odds? What impels patients and families to request that "everything possible" be done when a loved one's death is clearly imminent? Finally, why do we as a society continue to expect medical miracles, rather than viewing death as an inevitable, natural part of life?

There is no single answer to these questions. Yet, the broader philosophical and historical context in which they arise may shed some light on why futile treatments are used and why acknowledging futility has been so difficult. One factor leading to the use of futile treatment is undoubtedly our contemporary conception of disease and corresponding attitudes toward death. Western medicine tends to view disease as an enemy to be fought, with death marking the ultimate defeat in this battle against disease. Such a conception has historical roots in the mid-19th century, when American medicine first began to identify itself effectively with a more aggressive scientific approach.[30] It was also during this time that the germ theory of disease became predominant, with its emphasis on isolating and destroying a foreign organism. In contrast to ancient Greek physicians who saw disease as an imbalance within the body, modern western physicians picture disease as a war waged against outside invaders.

Susan Sontag depicted modern medicine in these terms when she ascribed the controlling metaphor in the description of fatal diseases, such as cancer, as drawn from the language of warfare[31(p64)]:

> [C]ancer cells do not simply multiply; they are "invasive" . . . "colonize" from the original tumor to far sites in the body, first setting up tiny outposts ("micrometastases"). . . . Rarely are the body's "defenses" vigorous enough to obliterate a tumor that has established its own blood supply and consists of billions of destructive cells. . . . the prospects are that "tumor invasion" will continue, or that rogue cells will eventually regroup and mount a new assault on the organism.

Likewise, the language of cancer treatment is infused with military images: in radiotherapy, "patients are 'bombarded' with toxic rays . . . chemotherapy is chemical warfare, using poisons"; all treatment aims to "kill cancer cells."[31(p65)]

A second factor that may contribute to a physiologic approach to end-of-life decisions is that the scientific method medicine employs tends to emphasize the physical signs of disease, while discounting the importance of patients' subjective experience of illness. According to some analyses, scientific medicine encourages a way of knowing in which people are seen as mechanical and deanimated. Thus, Hunter maintained that medicine "focuses on the measurable abnormalities of body and behavior that, by appearing regularly in cases of illness, are the indices of identifiable disease or injury."[32(p53)] Likewise, Keller argued that rather than encouraging empathic understanding or a "feeling for the organism," scientific medicine emphasizes the empirical observation of physical facts.[33] Downplaying the importance of patients' experiences and subjective quality of life can lead to the mistaken equating of survival with success.

Third, the use of futile treatments at the end of life may reflect our own fear of death. In modern secular society, such fear may center on fear of the unknown, as well as the loss of the comfort afforded by previous religious understandings. As Callahan notes elsewhere in this issue, in contrast to the Puritans for whom death was a religious and family event, to put in God's hands, modern Americans tend to find little solace or meaning in death.[34]

Fourth, to the extent that the culture of medicine encourages actions over omissions and judges attempts to beat the odds as "heroic," the tendency will be to continue to use futile interventions. To the extent that practicing medicine is equated with using treatments, rather than with implementing a plan of care (which may include both actions and omissions), the tendency will be to regard withholding or withdrawing treatment as "doing nothing" or, worse, "abandoning the patient."[35]

Fifth, treatments may continue to be used beyond the point of benefit to patients merely as a result of not deciding what to do. One physician poignantly described his most frequent response when faced with decisions about using futile treatments for dying patients as avoidance[36(p719)]:

> . . . not to make a conscious decision at all. . . . the problem is simply too difficult for me as a single human being to face in a conscious way. . . . On the other hand, how can I inflict the pain of aggressive treatment, and the suffering of further living, and spend the scarce resources of time and money on this person who is so obviously "trying" to die? And so, all too often, I don't make a conscious decision at all. I simply act, do something, make a decision without really considering the meaning of what I do.

Finally, whereas admitting medical futility requires acknowledging that medicine is sometimes powerless in the face of disease, continued efforts to beat the odds hold out the hope, however slim, of eventually mastering disease. As Nuland observed, fear of the loss and pain death portends can make it "more important to protect one another from the open admission of a painful truth [than to] achieve a final sharing that might have snatched an enduring comfort and even some dignity from the anguishing fact of death."[37(p244)] As a consequence, patients and families may keep up the charade of denial until the bitter end, clinging all the while to false hope, expecting to achieve a miraculous cure. Rather than exercising responsibility by educating patients and families about the hazards of excessive medical optimism, providers may instead prefer to put off such conversations indefinitely.

Conclusion

Those—dying then,
Knew where they went—
They went to God's Right Hand—
That Hand is amputated now
And God cannot be found—

The abdication of Belief
Makes the Behavior small—
Better an ignis fatuus
Than no illume at all
EMILY DICKINSON, 1845

Futile treatments can offer patients the illusion of continued life. They can offer families the false comfort of doing something. For health care providers, futile treatments may symbolize caring. Futile treatments thus perform vital functions; they are what Dickinson called an "ignis fatuus," something deluding or misleading that yet seems preferable to the absence of any understanding at all.

Despite their appeal, futile treatments should have no place in the humane care of dying patients. Although continuing to apply futile measures can offer a comfortable illusion, it is only by acknowledging, and moving beyond, futility that the dying process can become more dignified. Thus, when patients and families are no longer preoccupied with futile attempts to prolong life, they can turn their attention to preparing emotionally for death and to making practical decisions about the value of different settings for dying, such as the hospital, home, or hospice.[38] When health professionals are no longer preoccupied by futile technologies, they can focus instead on spending time with the patient and minimizing the patient's pain and discomfort. When those who surround the patient stop fighting for "everything" to be done, they can express love and concern in a more direct and meaningful way.[39] Only by redirecting our collective efforts in these ways will physicians help patients and make care of the dying a more honest and compassionate part of medical practice.

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Caring for Patients at the End of Life

Care of the Family When the Patient Is Dying

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Families shoulder many burdens during terminal illness. Their needs grow and change as their loved one's illness progresses. We describe specific physician behaviors that can assist families in coping with terminal illness. Early in serious illness, there are the emotional burdens of learning of the illness and coming to accept a terminal diagnosis, of giving up hope of cure. As terminal illness progresses, patients often need family members to help refocus hope despite the inevitability of death. Patients and families need support, guidance, and encouragement to begin planning for many decisions. Although emotional burdens are felt by most family members, families who choose to have their loved one die at home take on enormous direct caregiving burdens as well. They need information and supplies, including specific teaching of caregiving skills and logistic support. After the death of the loved one, family members have bereavement needs that require ongoing support.

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Most people do not endure a terminal illness alone. A family member or friend often accompanies the person along the entire trajectory of illness, from news that an illness may be life-threatening, to acceptance of the illness as terminal, through the final phases of the dying process, to the death itself. This may be a spouse, child or grandchild, some member of the extended biologic family, or, as in the lexicon of the AIDS [acquired immunodeficiency syndrome] community, a member of "the family of choice." For the purposes of this article, we have chosen the broadest possible definition of family: "Two or more people who share goals and values [and] have long-term commitments to one another" (*American Heritage Dictionary of the English Language*, 1992).

Recent literature details the tremendous burdens on families during serious illness. Families coping with serious illness shoulder substantial caregiving responsibilities.[1] They suffer considerable financial losses[2] and have increased rates of anxiety,[3] depression, and chronic illness.[4] Those caring for a loved one dying at home also experience a decline in physical and mental health.[5,6] This evidence lends support to the idea that families, as much as patients, need to be cared for during a patient's terminal illness.

Families bear many burdens during terminal illness. Their needs grow and change as their loved one's illness progresses, from the need for emotional support as they come to accept a terminal diagnosis, to specific anticipatory preparation for the final stages of their loved one's dying. After a patient's death, the family becomes the de facto primary recipient of care and has needs ranging from expressions of sympathy to referral for bereavement counseling.

The focus of this article is to guide physicians as they offer information, guidance, and support for family members of their dying patients.

News of a Serious Illness

Early in the course of a patient's serious illness, the long-term prognosis often is uncertain. Although death may be a possibility, some realistic hope of cure often continues to exist. During this initial phase, most medical efforts will focus on aggressive interventions aimed at curing the disease. This focus may divert the physician's attention away from both planning and the considerable comfort needs of both patient and family. The provision of adequate analgesia with opioids may be withheld because of a lack of a "terminal or hospice status."[7,8] Families often suffer from increased levels of anxiety or depression, yet may not attend to their own needs because they are concentrating on the ill family member.[4] Most families will face substantial financial losses or caregiving burdens.[2] Patients and families still pursuing active treatment with the hope of cure or prolongation of life, however, are usually ineligible for the comprehensive array of support services offered by hospice programs. They may be unprepared emotionally, as well.

As a patient's illness progresses, the prognosis worsens, and hope for cure diminishes. Considerable conflict may develop as various family members and the patient move at their own pace toward acceptance that the illness is terminal. Family members may have vastly different

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preferences as to the wisdom of continuing to focus on curative therapies. These conflicts can divert attention away from the increasing comfort needs of the patient. Such conflict may also prevent a timely discussion of the patient's wishes. At times, physicians will need to meet individually with family members to better understand the dynamics affecting decision making.

For some family members, the completion of advance directives and living wills may be seen as a recognition that the patient's illness is terminal and thus a step that they may not yet be ready to take. But excessive delay may produce a crisis situation in which a patient becomes incapacitated and the family must assume responsibility for clinical decisions in the absence of knowledge about the patient's preferences. The absence of planning often complicates an already difficult decision. Physicians play a vital role in helping patients and families to confront the possibility that death may occur.

Acceptance of Terminal Diagnosis

Coming to realize that a loved one's illness is terminal has been described as a "dawning acceptance."[9] Brief statements by physicians such as "Things are not going well" or "The tumor seems to be growing again" may begin to be heard as evidence of the inevitability of death. Visible signs of physical decline in a loved one often aid this process. Progressively, physicians need to openly discuss the reality of the terminal condition. Physicians are often faced with a need for both diplomacy and openness. They may begin with an explanation of the course of the illness and of the need to change the focus of treatment efforts. With time and support, families usually begin to make the transition from the hope of cure to more narrow goals. They begin to focus on the comfort of their loved one and the quality of life. They may hope that another holiday can be spent together, that a loved one's pain will be controlled, or that a family reconciliation will occur.[10]

Families typically welcome this discussion because most will have begun to confront this outcome. Even when most family members have accepted a terminal diagnosis, however, one or two members may persist in the belief in a cure. Other professionals may be consulted to help families in severe conflict. Families may benefit from an ultimate acceptance of death and the resolution of these conflicts.[11]

Family Needs During Terminal Illness

Family goals will change with the acceptance of terminal illness. Previously held dreams of cure will cede to more limited objectives: the desire for quality of life, to maximize comfort, and to reach certain milestones, birthdays, or anniversaries. Their needs will change as well, concomitant with changes in goals. Physician and other team member behaviors during the various stages of terminal illness can help—or hinder—families and the patient in achieving these goals.

Interviews with surviving family members suggest that some physician behaviors are particularly helpful to family members during a loved one's terminal illness.[9,11] Table 1 lists specific physician behaviors that families have identified as helpful.

TABLE 1.—*Family Needs During a Loved One's Terminal Illness*

Timely communication
Frequent and consistent communication
Gear communication to need
Encourage planning
Be aware of family conflict
Accommodate family's grief
Refocus hope
Remain available
Focus on patient's wishes
Attend to the comfort of the patient
Follow up with family after the death

Communication Should Be Timely

If patients and families are to make informed choices and provide mutual support, they need to be given information promptly and accurately. Family goals and choices may change radically in the face of a new prognosis. Postponing discussions of terminal illness or disease progression may only encourage false hopes and lead to inappropriate choices.[12]

At times patients may wish that their families not be informed of their illness. Although families may be understandably eager for news of their loved one's condition, physicians must respect a patient's right to privacy and obtain permission from patients before communicating with family members.

Communication Should Be Frequent and Consistent

In the emotional turmoil of a terminal illness, many things health care providers say will not be remembered. Despite repeated discussions, families may be much more confused than their physicians realize. Inconsistent information from different members of the health care team increases family confusion. Physicians can anticipate this need and be prepared to share information repeatedly with patients and their families, often answering the same questions two and three times.[13] The health care team must communicate frequently among themselves as well to ensure that a consistent message is presented to families.

Communication Should Be Geared to Need

Initially families may be ready only for news of serious illness and the potential for death. Time to reflect may be needed before a meeting to discuss the patient's prognosis. As the illness progresses, families need to be informed of the anticipated course—for example, how long their loved one might live, what limitations he or she might have, or what activities can be expected to be maintained. At later stages, more detailed instruction as to the final stages of death may be necessary.

Encourage Planning

Decisions to limit life-sustaining treatments often have to be made near the end of a patient's terminal illness. If preferences have been openly discussed with a loved one before this period, then decision making by family members will be greatly facilitated. The completion of living wills and advance directives may now be more familiar and acceptable to families following their use in the widely publicized deaths of Richard Nixon and Jacqueline Kennedy Onassis.

Many decisions remain for families following a death. These include questions of organ donation, autopsy, funeral, and burial plans. Whereas patients and families often wish to avoid or delay discussing these issues, planning lifts a burden from family members, who usually find it easier to "stand by" a loved one's wishes than to feel they are expected to "decide for" their loved one.

Be Aware of Family Conflict

As mentioned previously, we define "family" as broadly as possible. Patients with diseases that carry a strong social stigma, such as AIDS, may not have had contact with their biologic families for many years. Indeed, they may wish that some family members not be informed of their diagnosis. Some patients may have several competing families, such as a new wife and biologic children, each of whom questions the legitimacy of the other. In other cases, family members may be estranged from the patient and each other. Others may be incapable of confronting their loved one's illness and choose to withdraw. Physicians need to maintain an awareness of these dynamics.

The stress of terminal illness may exacerbate long-standing family conflicts. Obviously, these conflicts cannot be resolved simply and easily. But if left unrecognized, they may seriously complicate family decision making. The intervention of a social worker or chaplain can be valuable at these times. At other times, involvement of the hospital ethics committee may be beneficial.[14]

Accommodate the Family's Grief

Grieving before a loved one's death is a normal and necessary part of accepting a terminal illness. Recognizing and legitimizing these feelings with simple expressions of sympathy, such as "It must be difficult to watch your husband decline" or "I'm sorry your wife is dying," will acknowledge and respect their grief and can help encourage healthy grieving. It is often appropriate to acknowledge the frustration of the limitations of medical care.

Communication Should Refocus Hope

Even when the hope of cure is past, physicians can help families find hope and meaning in the passage of their loved one's remaining days. Families may find hope in all aspects of dying: that a spouse can remain comfortable and independent for as long as possible or that they can spend a last Christmas with the spouse. Physicians who adopt an attitude that equates death with failure or who inform families that "there is nothing left to do" only serve to remove that hope and prevent families from living fully until their loved one's death.

Remain Available

Families are in need of support and information throughout a loved one's terminal illness. Families fear that they will be unable to cope with their loved one's death, that symptoms will be uncontrollable, that death will be unmanageable, and that their wishes will not be heard. As the time of dying nears, it is tempting for physicians to withdraw, to feel as if their work is done, and that they have, in fact, failed. Yet this is a period of great emotional need, and the continued contact with a trusted physician can be of great solace.[15]

Focus on What the Patient Would Want

When a patient becomes incompetent, the burden of decision making will fall on members of the patient's family. Frequently decisions will be difficult, such as choosing to withdraw life support. Some families feel that their burden is increased when they are told that "the decision is yours." Advance directives and a durable power of attorney may give valuable direction and foundation for family decision making. If advance directives are unavailable, families can often identify and honor a patient's previous verbal directives. Discussions regarding treatment decisions are best focused on "what the patient would want."

The Doctrine of Substituted Judgment holds that a surrogate is assigned to carry out the wishes of an incapacitated person, not those of the surrogate's own preferences.[16] Families may wish to discuss in advance who the best surrogate might be, recognizing that it may not be a spouse or biologic next of kin, but might be a partner, lover, or other long-time friend.[17] Nevertheless, families should be encouraged to make decisions in consensus with and with the support and endorsement of the health care team so that no single person feels fully responsible for decision making.

Attend to the Comfort of the Patient

The greatest service a physician can provide to a family will often be skillful intervention in symptom control of a dying loved one. None of the growth and acceptance that characterize a "good death" are possible if patients and families are in constant crisis over uncontrolled suffering. A recent study documented the inadequacy of current pain management in terminal illness.[18]* Therefore, the provision of adequate analgesia with opioids and attention to other aspects of comfort remain paramount as illness advances.

Caregiving and Dying at Home

Given a choice, most patients prefer to die at home.[19] The home is generally a safe, comfortable, and familiar

*See N. MacDonald, MD, "Suffering and Dying in Cancer Patients—Research Frontiers in Controlling Confusion, Cachexia, and Dyspnea," on pages 278-286 of this issue.

place in which to die. For many families, caring for a dying loved one can be a wonderful opportunity for connection and healing and a demonstration of love and affection through daily acts of caregiving.

The physical and emotional burdens of caring for a dying loved one at home may be considerable, however, particularly when persons are expected to maintain other family and job responsibilities.[2] Physicians must be aware of these burdens and work with other health care professionals to aid families in obtaining adequate support for this effort.

Referral to a home hospice agency is helpful. Family caregivers have many needs that are best met before the final stages of illness. Timely referral provides the opportunity for necessary anticipatory education. Family caregivers need time to learn the myriad tasks required to provide optimal care. A multidisciplinary hospice team is particularly well suited to achieve this.

A nurse may visit and begin to instruct families on symptom recognition and appropriate interventions. Families learn to monitor a loved one's pain and adjust analgesic medications as needed. The nurse can teach personal care skills required when the dying person can no longer do self-care. The nurse can teach families what to expect during the final stages of dying. A physical therapist may visit and teach the family caregivers how to cope as the patient's functional abilities decline and can provide assistive devices as needed. Social workers may help with planning and assist families in adjusting to the changes in roles and family dynamics precipitated by terminal illness. A chaplain may be available to respond to spiritual needs.

Many crises may be successfully averted with appropriate planning. At times, however, despite the best efforts of all involved, a home caregiving situation may become untenable. The Medicare Hospice Act provides for admitting hospice patients to an institutional care setting if symptoms become uncontrollable. A five-day hospital stay benefit is also available with no justification for admission needed beyond that of providing respite for overburdened caregivers. Families may persist in struggling to maintain a loved one at home even as caregiving becomes unmanageable. These families can benefit from encouragement to relinquish the hope of a death at home without feeling that they have failed.

Callahan has written persuasively about the moral limits of our expectations for family caregivers.[20] Although death at home may fit our idealized version of a "good death" and may be the patient's strong desire, for many families this may not be realistic and may not be their preference.

Death in an Institutional Setting

Although more deaths are occurring at home, the preponderance of deaths in the United States still occur in an institutional setting. In these instances, physicians will often be responsible for communicating the news to the family. This role can be anxiety-provoking for many house officers and physicians because little formal training exists in this area. We have previously published guidelines for physicians and established a curriculum for medical students entering residency training.[21]

When an in-hospital death can be anticipated, advance notification of family members may allow them to be present at the time of death. Many survivors who are unable to be present at their spouse's death express strongly their desire to have been present.[11] If the attending physician or primary resident is not on call, families should be introduced to, or at least be notified of, the on-call physician's name. When death occurs, the physician should make a brief but unhurried examination to confirm the death and state plainly, "He (or she) has died." Jargon or euphemisms that may confuse survivors are best avoided. The physician should remain available after the death to answer questions. Providing a single, quiet room for grieving is critical. Often family members will wish to remain present with the deceased for some time following a death, and provisions should be made for this desire.

When a death is expected and families have agreed in advance, physicians may inform a family member or their designee over the phone. This designee may be a chaplain, friend, or neighbor who can go be with a surviving spouse or other family members who might otherwise be alone. A brief recounting of the final stages of life, "His heart began to weaken and finally stopped," followed by a concrete statement, "He has died," is recommended. An expression of sympathy, "I'm sorry," or reassurance, "His death was peaceful," is appropriate. Some time should be given for questions and expressions of grief, although when death is expected, these frequently are muted.

When death is unexpected, as may occur in 30% of patients,[22] less planning is possible, survivors' needs are greater, and much more care needs to be taken. Notification by phone often does not meet family needs. Rather, the family should be given brief medical information, such as "Your husband was in a car accident and seriously injured," and the family should be invited to come to the hospital as a group. This provides time to gather other family or friends for support and to ponder the real possibility that death may have occurred.

Occasionally distance or other obstacles may prevent families from coming to the hospital without great effort, risk, or sacrifice. These families may need to be informed directly of the death. At other times family members may ask directly, "Is he dead?" In this case, they should also be told the truth: "Yes, he is." Most ask a less direct question, "Is she OK?" Here it is usually preferable to again encourage the family to come to the hospital, while pausing to listen for a more direct question about death.

At the hospital, the physician should sit with the family, briefly explain the circumstances leading up to the death, and directly state that death has occurred. Because the family is unprepared for the death, expressions of grief will usually be much more pronounced, and questions will be frequent and repetitious. Providing a quiet, undisturbed private place for families is all the more important. Physicians and other health care providers can

expect to spend a prolonged time answering these questions and providing support.

Direct viewing of the deceased helps families to accept the reality of death, and they should be offered the opportunity to see their loved one. Privacy in viewing their loved one is also important and may require moving the deceased. Viewing the deceased is often retained as a graphic memory. Therefore, any trauma to the body due to accidental death or resuscitative efforts should be surgically dressed or otherwise concealed. Endotracheal tubes, intravenous lines, and any signs of blood should be removed, giving the family a more peaceful memory of the death.

Bereavement

It is after a patient dies that the family becomes the primary focus of care; it is also a time of ongoing family needs. Research suggests that spouses are at increased risk of morbidity and mortality during bereavement.[23] Yet, it is precisely at this time that minimal if any contact with their loved one's health care providers occurs. In our interviews with bereaved spouses a year after their loved one's death, 50% reported no contact with the patient's physician following the patient's death. Expressions of sympathy, a follow-up card, or a phone call had been greatly appreciated. Spouses who had received a card usually saved it and showed it to our interviewer, expressing much gratitude.[11] As a result of this investigation, our institution has implemented a program of routine contact with grieving families following a patient's death.[24]

Bereavement is uncomplicated in most situations. Many spouses, however, will be unprepared for the events of normal grieving. Physicians can assist grieving spouses by informing them that vivid dreams and tearful memories of the departed spouse may persist for several months and that a loss of interest in outside activities will likely persist for three to six months. Holidays, anniversaries, birthdays, and other special events may evoke particularly strong memories. Spouses should be encouraged to make special plans to be with family or other supportive persons during such times. Many may also take great comfort by joining a support group a few months after their spouse's death.

Some spouses are at high risk of complicated bereavement. Unexpected deaths, younger age, and previous psychiatric illness have all been linked with complicated or prolonged bereavement. Appropriate intervention in high-risk persons may prevent prolonged and complicated bereavement.[25] Clinicians need to maintain an awareness of this possibility and make appropriate referral when necessary.

Conclusion

Family needs change throughout terminal illness. Families need effective communication to help cope with and accept a terminal diagnosis. As the hope of cure diminishes, families need encouragement to plan ahead, to begin to focus on comfort and quality of life in place of prolongation of life. In the final stages of dying, families need physicians to not withdraw, to remain available for emotional support, and to provide ongoing assistance in symptom control. Following a loved one's death, grieving families need ongoing support from health care providers.

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Caring for Patients at the End of Life

Defining and Evaluating Physician Competence in End-of-Life Patient Care

A Matter of Awareness and Emphasis

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The issue of death and dying in the context of patient care, requisite knowledge, and clinical competence has received limited attention in America in the environment of medical education and residency training. National efforts toward reform in providing health care, coupled with public demands for more humanistic care at the end of life and for increasing physicians' accountability, reflect an atmosphere ripe for changing the attitudes of both the medical profession and society in caring for dying patients ("Report and Recommendations from the Board of Directors," American Board of Internal Medicine [ABIM] End-of-Life Patient Care Project, June 1995).

At first glance, evaluating physician competence in providing end-of-life patient care appears ponderous. The strategies for consideration are not unique, however. In fact, many of them are currently used to evaluate other aspects of clinical competence. Crucial to the process of evaluating physician performance is developing and disseminating a common definition so that all involved—both evaluators and evaluatees—understand what elements of clinical competence are being examined.

Defining the Competencies

In October 1993, ABIM initiated a small project on end-of-life patient care, an important goal of which included defining the scope of clinical competence expected of board-certified internists in the care of dying patients. The definition that has evolved from this initiative can apply to other specialties. It begins with the identification of core competencies: medical knowledge, skills in interviewing and counseling, use of the team approach, symptom and pain control assessment and management, professionalism, humanistic qualities, and medical ethics ("Resource Document on the Identification and Promotion of Physician Competency," ABIM End-of-Life Patient Care Project, October 1995). The specific components for each competency are further defined in Table 1 and supported by the literature.[1-15]

Evaluating Physicians

The traditional methods of evaluation described are placed in the framework of incorporating a greater emphasis on end-of-life patient care in concert with other areas of medical knowledge, content, and judgment on which physicians are tested and assessed.

Written Examinations

The most common approach to evaluation is the use of standardized written examinations featuring multiple-choice questions, particularly single-best answer (A-type) items such as those developed for board certification and recertification examinations. Components of competence in end-of-life patient care that are easily applied with this strategy are medical knowledge (palliative medicine, depression), symptom and pain control assessment and management (use of opioids or sedation, adjuvant analgesics, control of dyspnea), and medical ethics (advance directives, double effect, futility, nutrition and hydration). A spectrum of issues around which to develop test items includes terminating life-sustaining treatment and withdrawing or withholding life support, the right to refuse therapy, power of attorney for debilitated patients, terminal care, and implications and applications of living wills.

Many standardized written examinations also contain "core" questions. These are defined as items that test what physicians would be expected to know to provide basic patient care.[16] In that regard, end-of-life management issues should be considered valued and viable topics in the development and inclusion of core and noncore questions on certification examinations. Accordingly, the American Board of Medical Specialties should encourage its member boards to include related questions on their certification and recertification examinations.

In addition, including end-of-life patient care questions on national in-training examinations can help increase awareness in residency programs of the impor-

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TABLE 1.—*Physician Competencies and Definitive Components*

Components	*Core Competencies*
Medical knowledge	Palliative care Assessment and treatment of psychological distress Pharmacologic and nonpharmacologic treatment of pain and other symptoms
Interviewing and counseling skills	Listening Truth telling Discussing dying as a process Giving bad news Dealing with families of dying patients
Team approach	Understanding the multidisciplinary nature of end-of-life care—physician, nursing staff, social services, palliative care or hospice team, pharmacist, chaplain, patient, patient's family, patient advocate Promoting collegiality Enhancing ability of team members to fulfill professional responsibilities
Symptom and pain control assessment and management	Communication skills Comfort Use of opioids, sedation, or adjuvant analgesics NSAIDs Control of dyspnea, anxiety AHCPR and WHO guidelines
Professionalism	Altruism Nonabandonment Respect for colleagues Accountability Honoring patients' wishes Confidentiality Transference and countertransference
Humanistic qualities	Integrity Respect Compassion Courtesy Sensitivity to patients' needs for comfort and dignity
Medical ethics	Advance directives Do-not-resuscitate or do-not-intubate orders Nutrition and hydration Conflicts of interest Futility Double effect Surrogate decision making Physician-assisted suicide

AHCPR = Agency for Health Care Policy and Research, NSAIDs = nonsteroidal anti-inflammatory drugs, WHO = World Health Organization

tance of physician competence in this aspect of medical care. Many specialties, including internal medicine, neurology, and surgery, provide in-training examinations at regular intervals during residency. These examinations can signal a degree of preparedness for certification and can be useful in identifying the need for more intensive self-study strategies during the rest of training.[17] Similar emphasis is needed during medical school, and related medical knowledge and problem-solving skills should be assessed on parts II and III of the United States Medical Licensing Examination administered by the National Board of Medical Examiners.

Self-assessment

Another useful evaluation strategy is self-assessment; it is adaptable to many formats, including questionnaires, multiple-choice questions and essay examinations, and workbooks. This approach can be modified for both training environments and practice settings and can be designed to elicit attitudes about and confirm understanding of didactic material related to physician competence in caring for dying patients. Self-assessment also has a longtime linkage to continuing medical education—the American College of Physicians' Medical Knowledge Self-assessment Programs, for example—and in that venue can be used to reaffirm knowledge and the application of practical principles of palliative medicine and drug usage, the importance of communication skills, and understanding of alternative therapies. Educational videos are tools that also can be used in conjunction with both continuing medical education and structured self-assessment programs.[18]

A self-assessment survey was developed in conjunction with the ABIM End-of-Life Patient Care Project

TABLE 2.—*Preliminary Results of Residents' Self-assessment Survey—Reaction and Feelings After a Patient Died (n = 231)*

Representative Survey Questions	*Affirmative Response, %*
Feelings when their patient died	
Relieved that suffering had ended	39
Sad	36
Upset	18
Unaffected	9
Other	18
Reaction after their patient had died	
Took a break to regroup	49
Cried	37
Called or visited patient's family	27
Sent note of condolence or sympathy card	12
Attended patient's memorial service or funeral	10

and piloted during the summer and fall of 1995 in 55 internal medicine training programs. The survey is designed to seek residents' perceptions of personal experiences with dying patients, to identify opportunities for learning within the educational environment, and to offer recommendations that could improve physicians' patient care skills and level of professional comfort in caring for the dying. The 20-item survey focuses on a spectrum of issues, including residents' actual experiences with dying patients and families, perceptions of adequate training, self-evaluation of competencies, importance of health care team members, experiential autopsy acquisition, exposure to palliative medicine services, and recommendations to improve physicians' training.[19-22] One of the goals of the survey is to develop an instrument that could be used in primary care and general surgery training programs to gauge changes in clinical experiences and curriculum and, ultimately, to improve patient care.

Preliminary results from 12 programs with 231 residents responding (67% of 343) show that the instrument appears to be effective as a self-assessment tool. Five items from the 20-item survey are summarized briefly. Residents were asked at what levels of training did they participate with an experienced physician in a meaningful, influential discussion about death with a dying patient. Responses show that 55% had such experiences as medical students, 80% during the first year, 45% during postgraduate year 2, 21% during year 3, and 9% during year 4. Residents were asked to describe their experiences of end-of-life care with patients and their families and their perceptions of the quality of those experiences. Of the respondents, 63% indicated that their experiences were more positive, 31% felt that there were an equal number of positive and negative experiences, and 6% reported that they had more negative experiences. As noted in Table 2, residents were also asked how they felt when their patients died and what reactions were displayed.

In addition to self-rating their level of competence for each of the core components in end-of-life patient care, residents were asked whether they thought their training was adequate in 12 specific areas (Table 3). These early results show several areas where residents reported their training had not been adequate.

Finally, when asked about the importance of selective educational activities in conjunction with end-of-life care, residents identified experiences with role model clinicians as by far the most important educational component, followed by small group discussions, interdisciplinary conferences, grand rounds, and journal clubs.

Peer Evaluation

Assessment of physicians by professional colleagues can offer important and unique insights into clinical performance and the relationship between patients and physicians. The use of professional associate ratings provides both a practical method to assess humanistic qualities, communication skills, and professionalism and valid, reliable evaluation by peers—senior physicians, physicians-in-training, and nurses—of physicians' performance. Ten raters per physician-subject are needed to achieve validity and reliability of measurement.[23] Research shows that the ratings are not biased in a substantial manner by the relationship between the person being evaluated and the peer completing the evaluation.[24] The professional associate rating forms incorporate specific items on respect, integrity, and compassion—qualities that apply directly to the care provided by physicians to dying patients.

Other applicable descriptors to be rated on a professional associate rating form are a physician's "personal commitment to honoring choices and rights of others" and "appreciation of patients and their families' special needs for comfort and health."[23(p1659)]

Standardized Patients and Clinical Examinations

The use of standardized patients and objective structured clinical examinations provides other methods

TABLE 3.—*Preliminary Results of Residents' Self-assessment Survey—Adequacy of Training (n = 231)*

Thought Training Was Adequate	*Yes, %*	*No, %*
Controlling pain and related symptoms	82	18
Learning how to obtain DNR order	78	22
Telling patients they are dying	63	37
Telling patients what dying might be like	38	62
Informing patient's family of death		
Resident knew patient	78	22
Resident did not know patient	70	30
Talking to patient who requests assistance in dying or a hastened death	38	62
Declaring a patient dead	86	14
Talking to the family after patient has died	71	29
Requesting permission to do an autopsy	71	29
Requesting organ donation	60	40
Filling out death certificate properly	55	45

DNR = do not resuscitate

to assess communication skills, humanistic qualities, and professionalism within the context of end-of-life patient care. Standardized patients are nonphysicians trained to portray patients in a uniform and consistent manner. They can be asymptomatic; can have stable, abnormal findings on physical examination; or can simulate physical findings. Examinees interact with them as though they were interviewing, examining, and counseling real patients.[25]

Objective structured clinical examinations use a circuit of stations at which examinees are required to perform various clinical skills. These may include taking a brief history from a patient, doing part of a physical examination, undertaking a procedure, ordering or interpreting diagnostic studies, and counseling a patient. Objective structured clinical examinations provide a flexible approach to test administration in which various methods coalesce to obtain an assessment of clinical skills.[26]

Developed primarily to evaluate physical examination skills, standardized patients and objective structured clinical examinations can be used to measure skills in patient interviewing and counseling and rapport between physicians and patients.[25] To achieve reliability and validity in evaluating these particular skills, a range of 18 to 30 encounters with different patients is needed for each physician evaluated.[26,27] These methods are both time- and faculty-intensive in case development, administration, assessment, and feedback and are best conducted in structured and established settings within medical schools.

Evaluating Residency Programs and Health Care Delivery Systems

To ensure consistent educational opportunities in residency training and in the delivery of quality care to patients and their families facing the final chapter of life, evaluation is essential.

Residency Programs

One approach to evaluating residency programs recognizes the importance of establishing a baseline regarding the current emphasis placed on end-of-life patient care and then measuring the effect of curricular and experiential intervention. Recent studies show that within medical school and residency training, limited emphasis is placed on the teaching and training of physicians caring for dying patients, and few have formal curricula.[21,28,29] In fact, a review of current program requirements for accredited residency training (sponsored by the Accreditation Council for Graduate Medical Education) published annually in the graduate medical education directory shows no or only limited reference to formal training in end-of-life patient care. Relevant language from three specialties (family practice, internal medicine, general surgery) is described below[30]:

Family practice. Death and dying and the role of the family in illness management are defined as one of the principles of family practice.

Internal medicine. Issues of informed consent, living wills, patient advocacy, and related state laws concerning patients' rights are listed in the clinical ethics section of "Special Education Requirements."

Surgery. Educational conferences must include weekly review of all cases of current complications and deaths, including radiologic and pathologic correlation of surgical specimens and autopsies.

Greater emphasis could be placed on training residents in the care of dying patients by providing opportunities for learning during specific rotations in hospices and palliative care units and in other settings such as ambulatory clinics, support groups, and home visits.[31,32] Annual or biennial electronic literature searches, coupled with efforts by organizations committed to medical education to compile resource materials, could serve to validate innovation, change, and activity within educational and research environments.

Health Care Delivery Systems

As changes in health care delivery systems continue to be driven by market and managed care forces, coupled with pervasive budgetary constraints and government regulations, patient satisfaction should play an even greater role in shaping efforts and emphasis on quality of care, particularly at the end of life. Physician assessment in the 21st century will probably focus on the system of health care delivery and the performance of physicians within that system. Physician report cards may be used increasingly to measure performance.[33] Criteria for measurement often include severity of illness, comorbidity and case mix, and patient preferences. The customers and vendors of these report cards are hospitals and health care facilities, managed care organizations (nonprofit and for-profit health maintenance organizations), industry, and agencies such as the National Committee on Quality Assurance and the Joint Commission on Accreditation of Healthcare Organizations.

Within health care delivery systems, efforts are being made to determine patients' satisfaction with all aspects of health care plans. In that regard, patient satisfaction questionnaires have been refined over the past decade and are credible tools in helping assess the communication skills and humanistic qualities of physicians.[34] Increasingly, however, patient satisfaction questionnaires are intended to determine consumer satisfaction with health care plans and health care delivery systems and may reflect less emphasis on interactions with physicians and other health care professionals. These questionnaires can help identify the need for improvement in selective skills. Because assessments of physicians' skills can vary extensively from patient to patient, ratings from 20 to 40 patients are required to obtain a reproducible, meaningful assessment.[35] Given the large systematic relationships between patient characteristics, clinic sites, and ratings, caution must be exercised when comparing physicians who provide care in different settings, particularly if the age and health status of the patient population are dissimilar.[36]

Opportunities for Awareness and Action

Greater awareness is needed by the medical profession of the intrinsic role physicians can and should play in caring for and comforting dying patients and in consoling grieving families. Palliative medicine and hospice and home care are gaining recognition as separate, distinguished disciplines through increasing research, specialty organizations, federal legislation, quest for certification, and public demand. As a result, emphasis on end-of-life patient care will be enhanced in training and practice. These goals can be facilitated through the following targeted actions:

- Broaden the understanding of the core competencies necessary to provide end-of-life patient care;
- Profile the importance of educating physicians in end-of-life patient care as part of the agenda for national medical organizations;
- Include end-of-life patient care questions on national licensing and specialty in-training examinations and on certification and recertification examinations of member boards of the American Board of Medical Specialties;
- Assure that standards for accreditation of training programs offer opportunities for improving educational experiences in caring for patients in this final stage of life; and
- Promote a deeper understanding of the need for quality end-of-life patient care that will serve both the public and the profession well.

In conclusion, physicians' competence in end-of-life patient care can be assessed with a finite degree of validity and reliability. A definition, acceptance and understanding of specific competencies, and the application of traditional measures—the use of standardized written and oral examinations, standardized patients, peer evaluation, and patient satisfaction questionnaires—are required. Nonetheless, the judgment of physicians' competence may ultimately rest with the patients themselves and their families. Awareness by the medical profession and renewed emphasis within the educational and practice environments can make that much-needed difference.

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Caring for Patients at the End of Life

End-of-Life Treatment in Managed Care
The Potential and the Peril

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The conduct of end-of-life health care in managed care organizations is important, mysterious, and interesting. It is important because some form of managed care is involved in most health care provided in the United States.[1] Managed health care applies to many ways of organizing the provision and financing of health care, all of which have in common that they provide a specific set of health services to a defined group of people within a defined budget. This definition encompasses staff model health maintenance organizations, contractual relationships by which health care providers share the financial risk of providing health care to a health plan's members, and new forms of "integrated service networks." Health maintenance organizations (HMOs), preferred provider plans, and managed indemnity insurance cover 80% of the privately insured persons in the United States. Recent large-scale extensions of managed care to public programs of Medicare and Medicaid ensure the continued rapid growth of managed care. The raison d'être of managed care is to contain the growth of the cost of health care for groups of enrollees or to ensure that those costs do not exceed a predetermined budget.

Managed care plans cannot afford to ignore the cost of end-of-life care. About 10% of health care resources are used for the care of persons in their last year of life.[2,3] This percentage is higher for Medicare, which meets the needs of older people who have more long-standing disease and who are more likely to die. It is correspondingly lower in non-Medicare managed care groups. Patterns of end-of-life health care for chronically ill persons differ dramatically from those of persons who become suddenly ill before death. The latter primarily require hospital and physician services; the former use more long-term care and home care.[4] Patterns of care also vary from region to region, according to demography, the habits and evolution of local health care systems, and regulatory issues. The organization of managed end-of-life care varies greatly; no single set of concerns or guidelines will apply equally well to all plans.

As yet, little has been published about the current practices or potential for large-scale management of end-of-life care.[5,6] In addition, little has been published about the experiences of death and dying of patients in health plans. This may reflect the relative isolation of academic health centers from managed care. Some authors focus on the high cost of dying and on predicting which patients will have catastrophic costs.[7,8] There is no profile of the various courses of end-of-life care in various types of managed care organizations. The nature of hospice coverage in managed care contracts has not been systematically analyzed, except that it varies from none, to partial and disjointed, to comprehensive. Studies show that hospice, a form of managed end-of-life care, can be cost-effective and cost-saving, although the variety of institutional forms and changing patterns of use justify continued research.[9-12]

Managed end-of-life health care is interesting because its different financial organizations, relationships between primary and specialized providers, and incentives on health care professionals offer areas of concern and opportunities for improving this form of health care. In one view, managed end-of-life care threatens patients and families with rationing of important emerging therapies, limited access to costly beneficial treatments, impersonal bureaucracies, and physicians whose advocacy to patients' interest is tempered by financial conflicts of interest and "loyalty" to the managed care organization.[13] A brighter perspective is that the duty of managed care plans to provide comprehensive, longitudinal, and cost-effective care possibly offers a way out of the fragmented, bewildering, and uneven quality of the current health care system. It also decreases the incentive for health care professionals to overuse treatments, including those that clinicians, patients, and families might recognize as pointless, futile, or nonbeneficial in a setting of high-quality palliative care.

Possible Benefits of Managed End-of-Life Care

As part of a comprehensive and longitudinal health care system that integrates primary, specialized, and ter-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HMO = health maintenance organization

tiary care, managed care systems could improve the provision of end-of-life care.

Integrated Health Care

Managed care provides a framework and incentives for effective collaboration between the diverse kinds of providers and health care services that are needed for end-of-life health care. Traditional fee-for-service reimbursement assumes that providers will properly integrate care with other providers. Too often this expectation is not met in end-of-life care. Clinicians may not understand how to create multidisciplinary care plans. Primary care providers may lose contact with patients with progressive chronic diseases who are referred to specialists. Fee-for-service reimbursement may create a disincentive for a specialist to improve care by referring a patient to a primary care professional, home care, or hospice program if such referred patients do not return to the specialist. Patients too often report being cared for by oncologists or primary care physicians who have provided expert specialty care but who are uninterested, inaccessible, or unskilled in the final stages of home or nursing home care for a now-dying person.

Managed end-of-life care offers the opportunity of access to a spectrum of health care services and professionals who have incentives and institutional means to work together. The institutional and financial integration of care changes incentives toward the use of primary care physicians, advanced practice nurses, specialists, and teams. It decreases perverse incentives against timely hospice referrals, has the potential of leading to more effective institutional means of communication between teams of providers, and may enable persons near the end of life to make choices that are centered on patients' total treatment plans rather than on the interests of separate or even competing generalists or specialized professionals. It should decrease the preoccupation with certifying that patients have less than six months to live before being referred to hospice that now causes hospice care to be delayed until just before death[14] or to be underused for patients with non–cancer-related terminal illnesses. It will help patients and providers learn how to use the opportunities to improve care.

The shift to capitation-based, as opposed to service-based, financing may change the political landscape regarding public policy for end-of-life health care. Health plans may be more inclined to support legislative alternatives to physician-controlled delivery systems for end-of-life care or to promote more effective coordination between health care providers—such as laws regarding out-of-hospital do-not-resuscitate orders—that coordinate primary care orders with treatment by emergency medical systems.[15]

Portable Records for End-of-Life Treatment Plans

Managed care organizations interact with and coordinate many kinds of professionals caring for patients. The current health care system loses the large majority of advance directives as patients are transferred from clinics or nursing homes to hospitals.[16-20] Specialists or primary care providers may be unaware of the existence, location, or content of information about treatment or proxy preferences collected by other primary care professionals. Emerging electronic medical records offer the possibility of communicating the existence, location, or content of advance treatment or proxy plans or preferences to all professionals caring for a given patient. Such records, for example, could enable an emergency care provider to instantly become aware of the preferred proxy decision maker of an unconscious stranger arriving at an emergency department. The privacy and confidentiality issues with regard to electronic medical records must be addressed, however.[21]

Education About Planning End-of-Life Care

The fact that managed care organizations care for a large number of persons in a community creates an opportunity for new forms of community-based planning education. They are required to do so by the Patient Self-Determination Act.[22] Although such education will have modest influence on healthy persons to plan, it can substantially increase the number of frail or seriously ill persons who complete advance planning.[23-25] One managed care organization got 18.5% of its members to name a proxy by simply mailing a request and educational material.[26] Another study found that an HMO's patients with the acquired immunodeficiency syndrome (AIDS) were less likely than AIDS patients at an academic center to have advance directives.[27]

Enhanced Accountability for Quality

Models for managed health care systems presume that organizations linking diverse hospitals, clinics, and community-based services will use large-scale data systems to monitor the processes and outcomes of health care. Such data will be used internally to monitor and improve the efficiency and quality of care. Various reform proposals would make this information available to patients (in the form of "report cards") to inform choices of health plans and to government and academic agencies for health planning and technology assessment. Minnesota, for example, has created a "data institute" to collect data about health plans' costs, quality, access, utilization, and benefit structures.

The prevalence and cost of end-of-life care make it a high priority for scrutiny using these data systems. Managed end-of-life care organizations are well situated to examine and improve the quality of longitudinal, multi-institutional end-of-life health care for both acutely and chronically ill persons in various delivery

models—nursing home, community-based, or hospital clinic-based primary care.[28] Consumers and professionals could benefit from access to end-of-life report cards, for example, on pain control in patients with cancer and access to home care for all dying persons. Though it is doubtful that indicators of the quality of end-of-life care would, by themselves, influence patients to purchase a particular health plan, such indicators as part of an aggregate index of a plan's quality of health care could create a market incentive to improve end-of-life care.

Rationalizing Resource Allocation

Managed care organizations will undoubtedly seek to make end-of-life care more efficient and more rational. This will be difficult. Most authorities agree that advance planning to limit treatment, however beneficial from the standpoint of enhancing patient autonomy, will not reduce total health care costs.[24] Even so, they may make end-of-life care better and more to patients' preferences. Given the inconsistent use of advance directives by providers, some suggest that managed care systems could support patients' treatment preferences by not reimbursing for treatment that is provided after a clearly stated refusal.[15] One study of HMOs found that hospice care was cheaper than conventional medical care.[29] Health plans will participate in an overdue discussion of the definitions of medically necessary and appropriate care and medical futility. It is possible that health plan contracts[30] rather than laws will play a much larger role in how people articulate and "choose" the nature and limits of their legal claims on medical resources at the end of life.

Possible Perils of Managed End-of-Life Care

Divided Loyalty

Managed care plans do not, as yet, have the same beneficent obligation to individual patients that physicians do. They are expected to balance the needs of ill persons with the needs of enrollees who are potentially ill and who have comparable claims on a plan's resources and with their own balance sheet. Plans specify the services they cover and attempt to define medically appropriate, medically necessary, and experimental treatment to accomplish this balancing. Such balancing will be done with end-of-life care as well. Highly publicized conflicts over decisions to not cover autologous bone marrow transplants dramatize the problematic ethical credibility of health plans as resource allocators.[31] People are deeply suspicious of the motivations of insurance companies in making decisions to allocate or ration resources[32] and should rightly suspect that persons making general resource allocations will decide differently than persons with a bedside perspective.[33] Minnesota health insurers have used a variety of ways to allocate and ration the use of hospice care, visiting nurse care, respite care, and spiritual and psychological counseling for end-of-life care. The morality of such decisions is not unique to end-of-life care, but end-of-life care promises to be a hot spot for the debate about these issues.

Conflict of Interest

Health plans manipulate the credentialing of and incentives on health care professionals to meet financial goals. The credentialing affects the access of providers to reimbursement. The incentives may include bonuses for not providing or referring to costly services or contracts that attempt to limit what patients can be told about services that the plan does not wish to cover. The most troubling issue for end-of-life care in managed care is the possibility that clinicians are changed from being patients' advocates to having a personal stake in withholding treatment that would be in the patients' interests. Such conflicts destroy the trust that is the necessary foundation for good end-of-life care. The possibility that they might involve hospice providers who perform gatekeeping to hospital services or costly medicines like zidovudine (AZT) for persons with AIDS[34] properly causes great concern.

Devaluing Persons at the End of Life

Fee-for-service incentives create an incentive to care for and treat persons at the end of life even though many providers or society itself does not greatly value these persons or meeting their needs. Managed care poses potential threats to vulnerable, undervalued people who are ill suited to advocate for their own interests. First, in managed care budgets, the treatment of dying persons is a cost, not a revenue, except to the degree that choices for less expensive palliative care offset the greater costs of hospital or high-tech treatment.[9,35-37] Prolonged labor- and technology-intensive palliative care is expensive even if it does lead to a better-quality death. Managed care budgeting has the dangerous potential of aligning the economic incentives for treating dying or chronically ill persons with social prejudices against them. The worst possibility would be a managed care system that limits access to both hospital and nursing home care in favor of home care and then provides inadequate community-based home care as well.[38] Second, the corporate culture of large managed care organizations may adversely affect the possibility of humanistic alternatives to institutionally managed end-of-life care.[39,40] Though few would argue against technologies that improve the quality of end-of-life care, the hospice movement has renewed such care by its example of personal, small-scale, and charismatic institutions. The bureaucratic consolidation of end-of-life care in large managed care systems[6] should not foreclose this kind of humane and prophetic challenge to health care professionals or this kind of hope for dying persons and their loved ones.

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In Memoriam

California Medical Association

Blees, Kristie Sherwood, Sacramento. Died Jun 15, 1995, aged 42. Graduate of Medical College of Wisconsin, Milwaukee, 1987. Dr Blees was a member of the Sacramento-El Dorado Medical Society.

Clark, Howard E., Monterey. Died Jun 17, 1995, aged 95. Graduate of University of Minnesota Medical School, Minneapolis, 1929. Dr Clark was a member of the Monterey County Medical Society.

Cotchett, John Craig, San Mateo. Died July 30, 1995, aged 46. Graduate of Northwestern University of Medical School, Chicago, Illinois, 1974. Licensed in California in 1983. Dr Cotchett was a member of the San Mateo County Medical Association.

Edwards, Robert L., San Francisco. Died Apr 6, 1995, aged 79. Graduate of University of Cincinnati, Cincinnati, Ohio, 1943. Licensed in California in 1944. Dr Edwards was a member of the San Francisco Medical Society.

Ellwood, Paul, Oakland. Died Apr 20, 1995, aged 95. Graduate of Rush Medical College, Chicago, Illinois, 1925. Licensed in California in 1926. Dr Ellwood was a member of the Alameda-Contra Costa Medical Association.

Gibbons, Ross Matthew., Vallejo. Died Jul 20, 1995, aged 78. Graduate of University of California, San Francisco, School of Medicine, 1941. Licensed in California in 1942. Dr Gibbons was a member of the Solano County Medical Society.

Hartman, Brady Chambers, San Diego. Died Jun 13, 1995, aged 59. Graduate of University of Miami School of Medicine, Miami, Florida, 1968. Licensed in California in 1970. Dr Hartman was a member of the San Diego County Medical Society.

Levine, Richard B., Santa Ana. Died Jul 6, 1995, aged 56. Graduate of University of Illinois College of Medicine, Chicago, 1963. Licensed in California in 1969. Dr Levine was a member of the Orange County Medical Association.

Miller, Earl R., San Francisco. Died Jun 24, 1995, aged 87. Graduate of University of Wisconsin Medical School, Madison, 1936. Licensed in California in 1937. Dr Miller was a member of the San Francisco Medical Society.

Mulville, Maurice F., Fullerton. Died Jun 20, 1995, aged 84. Graduate of Tufts University School of Medicine, Boston, Massachusetts, 1937. Licensed in California in 1947. Dr Mulville was a member of the Orange County Medical Association.

Pingree, Louis J., San Jose. Died Aug 3, 1995, aged 79. Graduate of Stanford University School of Medicine, Stanford, California, 1944. Licensed in California in 1944. Dr Pingree was a member of the Santa Clara County Medical Association.

Raskind, Robert, Bakersfield. Died Jul 6, 1995, aged 81. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1938. Licensed in California in 1941. Dr Raskind was a member of the Kern County Medical Society.

Root, Irving, San Bernardino. Died Jun 28, 1995, aged 65. Graduate of University of California, San Francisco, School of Medicine, 1953. Licensed in California in 1954. Dr Root was a member of the San Bernardino County Medical Society.

Ruesch, Jurgen, San Francisco. Died Jul 9, 1995, aged 85. Graduate of University of Zurich, Switzerland, 1935. Licensed in California in 1944. Dr Ruesch was a member of the San Francisco Medical Society.

Shapiro, Howard A., San Francisco. Died Jul 24, 1995, aged 64. Graduate of Pritzker School of Medicine, University of Chicago, Chicago, Illinois, 1955. Licensed in California in 1957. Dr Shapiro was a member of the San Francisco Medical Society.

Vannucci, Oliver R., Stockton. Died Jul 5, 1995, aged 77. Graduate of University of California, San Francisco, School of Medicine, 1942. Licensed in California in 1942. Dr Vannucci was a member of the San Francisco Medical Society.

Wahlen, Donald E., Visalia. Died Jul 12, 1995, aged 66. Graduate of Loma Linda School of Medicine, Los Angeles, California, 1955. Licensed in California in 1956. Dr Wahlen was a member of the Tulare County Medical Society.

Whiting, E. Gale, Berkeley. Died Jul 22, 1995, aged 87. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1933. Licensed in California in 1934. Dr Whiting was a member of the Alameda-Contra Costa Medical Association.

Wybel, Robert E., Bakersfield. Died Jun 21, 1995, aged 72. Graduate of Harvard Medical School, Boston, Massachusetts, 1946. Licensed in California in 1962. Dr Wybel was a member of the Kern County Medical Society.

Young, Clarence J., Apple Valley. Died Jul 14, 1995, aged 78. Graduate of University of Chicago Medical School, Chicago, Illinois, 1953. Licensed in California in 1955. Dr Young was a member of the San Bernardino County Medical Society.

New Mexico Medical Society

Fitts, Ralph L., Albuquerque. Died Jun 13, 1995, aged 95. Graduate of Rush Medical College, Chicago, Illinois, 1935. Licensed in New Mexico in 1975. Dr Fitts was a member of the Greater Albuquerque Medical Association.

Hunt, William, Las Cruces. Died May 3, 1995, aged 74. Graduate of University of Minnesota, Minneapolis, 1945. Licensed in New Mexico in 1980. Dr Hunt was a member of the Dona Ana County Medical Society.

Kepler, M. Oliver, Espanola. Died Mar 27, 1995, aged 75. Graduate of State University of New York, Syracuse, 1949. Dr Kepler was a member of the Rio Arriba County Medical Society.

McPheron, William G., Hobbs. Died Aug 2 1995, aged 77 Graduate of University of Oklahoma, Oklahoma City, 1942. Licensed in New Mexico in 1958. Dr McPheron was a member of the Lea County Medical Society.

Ortiz, Michael P., Albuquerque. Died Jul 26, 1995, aged 39. Graduate of University of New Mexico School of Medicine, Albuquerque, 1989. Licensed in New Mexico in 1993. Dr Ortiz was a member of the Greater Albuquerque Medical Association.

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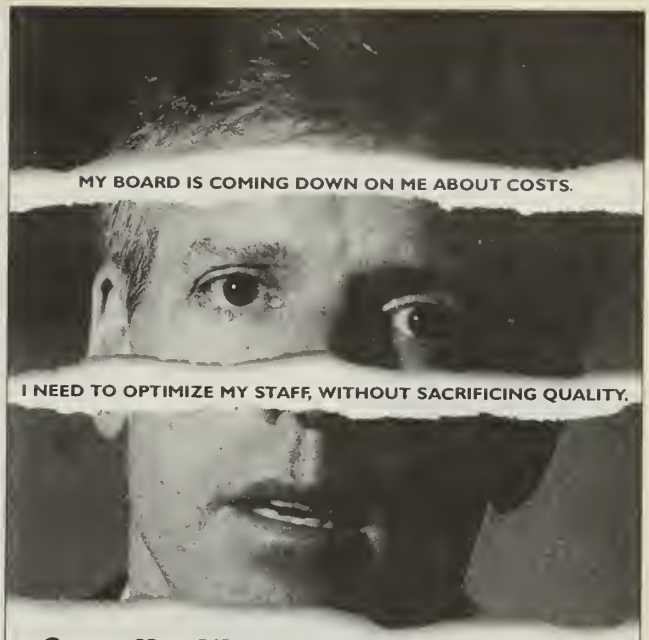

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(Buchwald D, Manson SM, Brenneman DL, et al: Screening for depression among newly arrived Vietnamese refugees in primary care settings. West J Med 1995; 163:341-345)

A brief, culture-specific, self-report screening measure for depression, the Vietnamese Depression Scale, was used to determine the prevalence of depressive symptoms among 1,998 consecutive adult Vietnamese refugees who presented at 10 public health clinics within 2 months of their arrival in the United States. Of these patients, 6% met the criterion for a probable case of depression ("positive"). Being divorced, separated, or widowed and poorly educated were strongly associated with a greater likelihood of screening positive. Somatic complaints were common and induced considerable anxiety about physical health status. Nearly a third of the patients reported sadness and dysphoria; culture-specific symptoms of depression also were prevalent. Our findings document the feasibility of screening for depression using the Vietnamese Depression Scale among Vietnamese refugees, particularly in primary care settings where they are first likely to be seen by health professionals after arrival in their host country.

DEPRESSION **CROSS-CULTURAL**
VIETNAMESE

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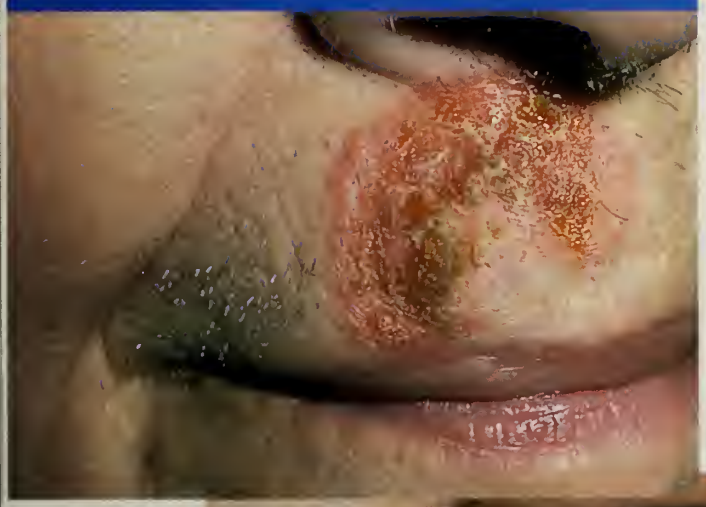

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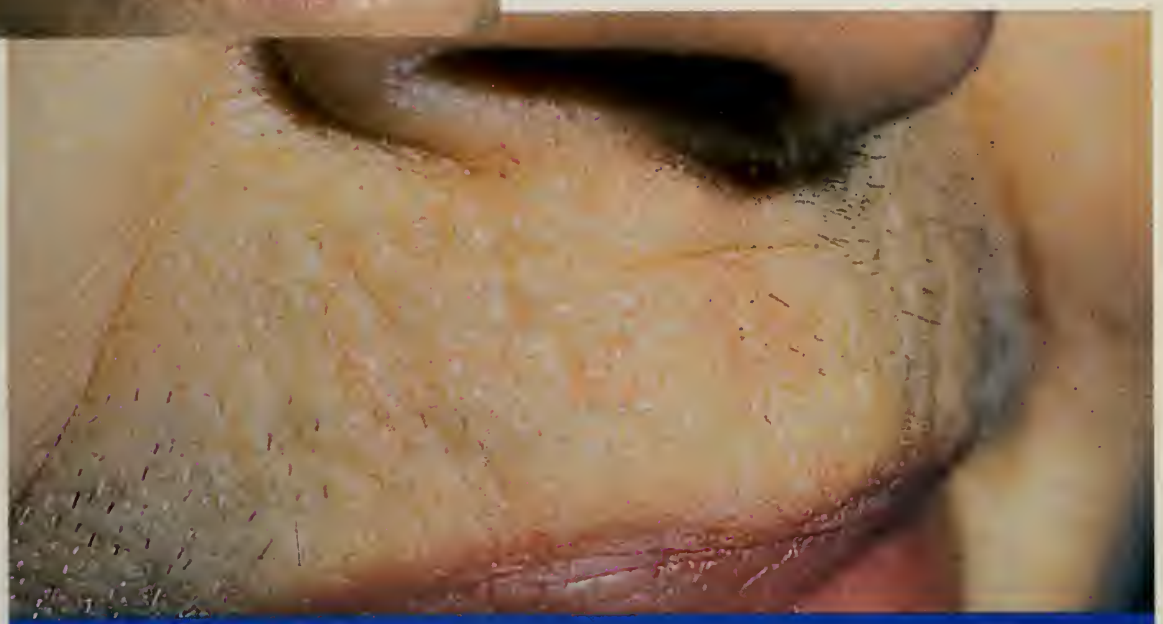

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2. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. *Pediatrics.* 1992;89:210-214.
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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 27-28—**Ethics in Managed Care Conference.** Samaritan Health Services at the Buttes Hotel, Phoenix. Fri-Sat. Contact: Linda Luzader, (602) 495-4936.

October 27-29—**Arizona Orthopaedic Society—Scientific Meeting**. Maricopa Medical Center at Westin La Paloma, Tucson. Fri-Sun. Contact: Patrice Hand, (602) 246-8901.

November 1-4—**AMTA Methadone Conference**. University of Arizona College of Medicine at The Pointe Hilton, Phoenix. Wed-Sat. Contact: U of A.

November 2-4—**Eighth Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 2-5—**24th Annual Alex Newman Radiology Conference: Abdominal Imaging and MRI**. Maricopa Medical Center at the Camelback Inn, Scottsdale. Thurs-Sun. Contact: (602) 267-5366.

November 4—**Audiology Videoconference**. Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 4—**Recent Developments in Mood Disorders**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Sat. Contact: U of A.

November 5—**Career Choices.** American College of Physician Executives at the Westin La Paloma, Tucson. Sun. Contact: (800) 562-8088.

November 5-10—1995 **Annual Meeting, American Urological Association, Western Section.** Phoenician Resort, Scottsdale. Sun-Fri. Contact: (714) 898-9155.

Noveber 6-10—**Physician in Management Seminar I.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 6-10—**Physician in Management Seminar II.** American College of Physician Executives at Westin La Paloma, Tucson. Mon-Fri. Contact: (800) 562-8088.

November 16-19—**Controversies in Critical Care**. Society of Critical Care Medicine at the Pointe Hilton Resort on South Mountain, Phoenix. Thurs-Sun. Contact: (714) 282-6000.

November 17—**Arthritis Update.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Fri. Contact: U of A.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 18-19—**Workshop on Transesophageal Echocardiology.** American Society of Anesthesiologists at the Marriott's Camelback Inn, Scottsdale. Sat-Sun. Contact: (708) 825-5586.

December 2—**ENT for the Specialist**. Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 11-14—**6th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Thurs-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 16-20—**Phoenix Surgical Society—24th Annual Meeting**. Phoenician Resort, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

January 19-21—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

Fehruary 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 11-15—**International Congress IX on Endovascular Interventions.** Arizona Heart Institute and International Society for Endovascular Surgery at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: Erika Scott, (602) 266-2200.

February 12-16—**5th Annual Psychopharmacology Review**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

February 15-17—**Mayo Interactive Surgical Symposium**. Mayo Foundation at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Trish Gean, (602) 301-8323.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 30-February 3—**34th Annual Scientific Session of the Western Society of Allergy and Immunology**. Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, P.O. Box 1122, Roanoke, TX 76262. (817) 491-2616.

ANESTHESIOLOGY

November 3-5—**Anesthesiology Update: 1995**. UCD at Monterey Plaza, Monterey. Fri-Sun. 12 hrs. $300. Contact: UCD.

January 10-13—**UCSD Anesthesia Update**. UCSD at Hotel del Coronado. Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 11-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. 2 wks. 20 hrs. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City, CA 94404. (800) 345-3691.

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

(Continued on Page 332)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 330)

March 26-29—**5th John J. Bonica Hawaii Pain Conference**. Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

November 18—**14th Annual Sharrer Symposium: Progress in Cardiology**. Kaweah Delta Hospital District at Visalia Convention Center. Sat. 6 hrs. Contact: Barbara Porter, RN, (209) 625-7106.

December 8-10—**13th Annual Advances in Heart Disease: An International Perspective.** American College of Cardiology at San Francisco. Fri-Sun. 16.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

December 9—**Cardiac Therapeutics.** USC at Ritz-Carlton, Laguna Niguel. Sat. 8 hrs. $75. Contact: USC.

January 26-28—**Clinical Nuclear Cardiology: Case Review With the Experts**. Cedars-Sinai Medical Center at Los Angeles. Fri-Sun. 17.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

EMERGENCY MEDICINE

November 11-12—**Biomechanics of Trauma**. UCSD at Le Meridien Coronado. Sat-Sun. 11 hrs. $200. Contact: UCSD.

November 13-17—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 3-8—**16th Annual Current Concepts in Emergency Care**. American College of Emergency Physicians at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269.

December 11-15—**Emergency Medicine Symposium II**. UCSD at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 18-20—**California Trauma Conference**. UCD at Hyatt Regency, Sacramento. Thurs-Sat. 17 hrs. $425. Contact: UCD.

February 24-March 2—**Pediatric Emergencies**. UCSD at Royal Lahaina, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

November 6-8—**Geriatrics Update 1995.** Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

December 7-9—**Clinical Care of the AIDS Patient**. UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 24 hrs. $395. Contact: UCSF.

December 9-11—**Bone Mass Management in Osteoporosis and Other Bone Diseases.** National Osteoporosis Foundation at the Biltmore Hotel, Los Angeles. Sun-Mon. 14 hrs. Contact: NOF, 1150 17th St NW, Ste 500, Washington, DC 20036-4603. (202) 223-2226.

January 20-27—**Sports Medicine.** UCSD at Royal Waikoloan, Kona, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

January 26-28—**Primary Care Dermatology**. UCSD at Hilton Beach and Tennis Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: UCSD.

February 1-3—**Neurology for the Non-Neurologists.** UCSD. Thurs-Sat. 21 hrs. $500. Contact: UCSD.

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

March 20-22—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 15 hrs. $325. Contact: UCSF.

INFECTIOUS DISEASE

November 3-5—**Advances in Infectious Disease**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

November 3-4—**6th Annual Practical Methods of Diabetes Management**. MMC/UCI Center for Health Education at Sutton Place Hotel, Newport Beach. Fri-Sat. Contact:Center for Health Education, (310) 933-3811.

November 10-11—**American College of Physicians: Northern California Regional Scientific Meeting**. American College of Physicians at Sir Francis Drake Hotel, San Francisco. Fri-Sat. 11 hrs. $150-$170. Contact: Carol Finley, St Mary's Medical Center, (415) 750-5955.

February 9-10—**Advances in Diagnosis and Treatment of Splenic Disorders.** Cedars-Sinai Medical Center at Hotel Sofitel Los Angeles. Fri-Sat. 11.5 hrs. Contact: Bari Laner, Cedars-- Sinai Medical Center, 8700 Beverly Blvd., Room 2211, Los Angeles 90048. (310) 855-2937.

February 14-16—**29th Annual Recent Advances in Neurology**. UCSF at Sheraton Palace Hotel San Francisco. Wed-Fri. 15 hrs. $375. Contact: UCSF.

February 17-22—**Topics and Advances in Internal Medicine**. UCSD at San Diego Marriott. Sun-Thurs. 50 hrs. $595. Contact: UCSD.

NEPHROLOGY

November 9-10—**International Symposium on Continuous Renal Replacement Therapy.** UCSD. Thurs-Fri. Contact: UCSD.

January 31-February 3—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Regency on the Bay San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

November 10-12—**Current Issues in Perinatal Medicine**. MMC/UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Fri-Sun. Contact: Center for Health Education, (310) 933-3811.

December 1-2—**Controversies in Hormones, Menopause and Breast Cancer**. MMI/UCI Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

December 7-10—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's, Las Vegas. Thurs-Sun. $295. Contact: Center for Continuing Medical Education, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

February 10-13—**51st Annual Postgraduate OB/GYN Assembly**. Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Sat-Tues. 22 hrs. Contact: Director, 5820 Wilshire Blvd #500, Los Angeles 90036. (213) 937-5514.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Educaton Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 825-6774.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (213) 342-1544.

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Articles

Improving Identification of and Intervention for Alcoholism

PHILIP S. MEHLER, MD; MICHAEL D. McCLELLAN, MD; DENNIS LEZOTTE, PhD; EDMUND CASPER, MD; *and* PATRICIA A. GABOW, MD, *Denver, Colorado*

A retrospective hospital medical record review was done using 45 diagnoses or laboratory findings that are associated with alcohol abuse. The reviewer assessed the level of documentation of alcohol consumption in relation to alcohol-related disorders before and after an intervention to heighten house staff's recognition of alcoholism. Of the patients with at least 1 alcohol-related disease, 58% were explicitly asked about their consumption of alcohol. The mean number of alcohol-related diseases was 3.8 ± 2.3 in the group questioned compared with 1.9 ± 1.4 in the group not asked ($P < .01$). After the intervention, 90% of patients with at least 1 alcohol-related disease were asked about alcohol consumption. Once again, those asked had an average of 3.9 diseases compared with 2.1 in the other group ($P < .01$). Only younger age, increased specificity of alcohol-related disease, and the promotion of physician awareness were important factors for influencing documentation. Introducing a program for detecting alcoholism can have a beneficial effect on physicians' identification of alcoholism in patients with alcohol-related illnesses.

(Mehler PS, McClellan MD, Lezotte D, Casper E, Gabow PA: Improving identification of and intervention for alcoholism. West J Med 1995; 163:335-340)

Alcoholism is a serious disease with an alarmingly high prevalence in society. Estimates of alcohol-related deaths are as high as 100,000 per year in the United States.[1] The primary causes of death in men aged 25 to 44 years are alcohol linked.[2] After heart disease and cancer, alcoholism is America's third largest health problem, costing $100 billion per year.[3] Patients with alcohol problems constitute 25% of all patients admitted to a hospital.[4] Chronic liver disease due to alcohol abuse is the 11th leading cause of death in the United States.[5] Moreover, the alcohol trauma syndrome is an enormous problem[6]; 41% of trauma patients from a major trauma center have been reported to have measurable blood alcohol concentrations on initial evaluation in emergency departments.[7]

Despite the magnitude of the alcohol abuse problem, alcoholism is an underdiagnosed and undertreated problem. It has been estimated that only one in ten patients with alcoholism is properly diagnosed.[8] In a prospective medical record audit from the University of Colorado Health Sciences Center, an alcohol use history was not even recorded in 22% of hospital records.[9] Only 45% of inpatients screening positive with the Michigan Alcoholism Screening Test (MAST) had chart notes indicating or diagnosing alcoholism as a problem.[10] Similarly, physicians in outpatient settings are also ineffective at identifying patients with less serious alcohol-related problems.[11] Among a group of employees whose drinking was serious enough to be identified on the job, less than a quarter recalled physicians' warnings, even though more than three fourths had seen a physician in the preceding year.[12] Unfortunately, even after numerous questionnaires for detecting alcoholism have been developed, physicians continue to overlook this disorder in their patients.

None of the published studies have addressed the adequacy of the alcohol history in a patient with medical diseases that are potentially alcohol related. It might be anticipated that a more adequate history regarding alcohol abuse would be obtained in patients entering a county hospital with disorders such as pancreatitis, rhabdomyolysis, thrombocytopenia, or subdural hematomas.

To address this hypothesis, we did a sequential study. Our goal was to determine how medical house staff at an urban hospital perform in assessing the connection of alcohol to certain disease states that can be alcohol related before and after programs emphasizing the importance of alcoholism identification and treatment were introduced.

Patient Records and Methods

This study was a retrospective inpatient medical record review. We identified 45 diagnoses or laboratory findings, based on recent published articles, that should

From the Department of Community Health Services (Dr Mehler) and the Division of Renal Diseases (Dr Gabow), Department of Medicine (Dr McClellan), and Department of Psychiatry (Dr Casper), Denver General Hospital; and the Department of Preventive Medicine and Biometrics (Dr Lezotte), University of Colorado School of Medicine, Denver.

Reprint requests to Philip S. Mehler, MD, Dept of Community Health Services, #0146, Denver General Hospital, 777 Bannock St, Denver, CO 80204.

ABBREVIATIONS USED IN TEXT

CAGE [test] = Need to *C*ut down on your drinking?
*A*nnoyed by criticism about your drinking?
*G*uilty about drinking?
Need a morning drink or *E*ye-opener?
MAST = Michigan Alcoholism Screening Test
SD = standard deviation

trigger a suspicion of alcohol use.[13-20] These alcohol-related disorders were divided into three levels: level 1 were those that were strongly suggestive, level 2 were suggestive, and level 3 were consistent with the diagnosis of alcoholism (Table 1). Disorders in level 1 are either found only with alcohol abuse, or alcoholism is the leading cause of this particular medical problem. They have a high discriminatory power for the diagnosis of alcohol abuse. Level 2 disorders lack this high specificity for alcohol abuse, but are frequently found in association with it. Level 3 diagnoses, while consistent with alcohol abuse, are frequently caused by some other independent medical condition.

Physicians reviewed medical records to establish the presence of one or more of these alcohol-related diseases. The reviewers assessed the level of documentation of historical details of alcohol consumption to establish how frequently patients were referred for further evaluation or treatment. During the initial phase of the study (July 1, 1984, to August 21, 1984), records of 182 consecutive patients admitted to Denver (Colorado) General Hospital were retrieved for review by two physicians. Similarly, after the intervention, a subsequent review of the records of 135 patients (from July 1, 1985, to August 21, 1985) was done. The 12 house staff involved in caring for these patients during each of the two years of the study were not the same people.

The intervention before the second study period involved an intensive alcohol education effort. Specifically, this involved having a psychiatrist from the alcohol consultation service attend all Department of Medicine morbidity and mortality conferences to emphasize sequelae of alcoholism among this patient population. The guidelines for court-ordered alcohol treatment and the process for formal alcohol consultation were given to each house-staff officer at the beginning of each rotation. A modified CAGE form (an acronym derived from 4 questions: Have you ever felt that you should *C*ut down on drinking? Have people ever *A*nnoyed you by criticizing your drinking? Have you ever felt *G*uilty about your drinking? Have you ever had a drink first thing in the morning to help yourself feel better or to get rid of a hangover [*E*ye-opener]?), which is a short screening test for alcoholism,[21,22] was placed on each medical patient's chart as a reminder to the house staff. Also, alcoholism as a primary medical problem was emphasized at the morning report by the staff and chief medical residents in attendance.

Statistical Analysis

Student's t tests or nonparametric equivalents (Wilcoxon signed-ranked test), or both, were performed on continuous variables to compare groups where appropriate. Categorical variables were compared using χ^2 tests. Stepwise logistic regression was used to identify

TABLE 1.—*Levels of Alcohol-Reloted Disorders Ronging From Strongly Suggestive (Level 1) to Consistent With o Diognosis (Level 3) of Alcoholism*

Level I	*Level 2*	*Level 3*
Pancreatitis	Gastritis	Esophagitis
Alcoholic hepatitis	Ethylene glycol intoxication	Esophageal carcinoma
Cirrhosis	Methylene intoxication	Hemorrhoids
Ascites without tumor	Rhabdomyolysis	Atrial fibrillation, transient
Spontaneous bacterial peritonitis	Diabetes mellitus due to chronic pancreatitis	Unexplained cardiomyopathy
Alcoholic ketoacidosis	Folic acid deficiency	Aspiration pneumonia
Macrocytosis	Thrombocytopenia	Lung abscess
Wernicke's encephalopathy	Coagulopathy	Tuberculosis
Alcohol blood level	Hypersplenism	Hypocalcemia
Hepatorenal syndrome	Peripheral neuropathy without apparent cause	Impotence
	Subdural hematoma	Iron deficiency anemia
	Multiple skeletal fractures	Seizure disorder
	Gunshot or stab wound	Autonomic insufficiency without apparent cause
	Hypophosphatemia	Acute delirium without known drug cause
	Cerebral atrophy unrelated to age	Depression
		Suicide attempt
		Strong family history of liver disease
		Hypomagnesemia
		Pancreatic calcifications
		Low blood nitrogen level

TABLE 2.—*Study Patients Who Were or Were Not Asked About Alcohol Use When Admitted to a Hospital, Before (Group I) and After (Group II) Increased Physician Awareness Program*

	Study Group I			Study Group II		
Potient Chorocteristics	*Potients, No.**	*Age, yr**	*Alcohol-Reloted Disorders, No.**	*Potients, No.**	*Age, yr**	*Alcohol-Reloted Disorders, No.**
No alcohol-related disorder	50	51.3	0	66	49.2	0
Alcohol-related disorder (ARD)	132	49.5	2.35	131	45.7	2.02
ARD not questioned	55	51.5	1.90	13	57.1	2.31
ARD questioned	77	48.8	3.86	118	44.5	2.88
Detailed questioning about ARD	44	48.8	5.10	50	45.2	3.90
Brief questioning about ARD	33	48.7	2.18	68	44.1	2.10
Referred for treatment	18	46.5	5.20	31	40.3	3.87

*The number given is the mean.

significant predictive factors that influenced a physician's action to document alcohol-related illness, where the outcome was the dichotomous variable "documented" versus "nondocumented." The primary predictive factor of interest differentiates the period before the intervention from the period after the intervention. The initial factors included in the model consisted of time period, race, sex, age, and the severity of the alcohol-related disease, each considered to influence the final action of physicians to document an alcohol-related illness. Factors remained in the model if they achieved a .05 level of significance.

Results

Before Intervention

During the first half of the study, 105 men and 77 women made up the study group. Of this "group I," 132 of 182 patients (72.5%) had one or more of the diagnoses or abnormalities considered possibly alcohol related. This cohort consisted of 82 men and 50 women with a group mean age of 49.5 years (standard deviation [SD], 17.0; range, 18 to 93). The remaining 50 patients (23 men and 27 women) with a similar mean age of 51.3 (SD, 20; range, 18 to 90) were admitted for disorders not considered to be associated with alcohol abuse (Table 2).

Of these 132 patients with an alcohol-related diagnosis, 77 (58%) were explicitly asked by either an intern or a resident about their consumption of alcohol. The mean age of these 77 patients was not different from that of the 55 patients not questioned about alcohol use. The mean number of alcohol-related diagnoses was 3.8 ± 2.3 in the group questioned compared with 1.9 ± 1.4 in the group not asked about alcohol use ($P < .01$). Of the 77 patients who had at least one alcohol-related illness and who were asked if they consumed alcohol, only 44 (57%) were asked more extensive questions about the quantity of alcohol consumed and any legal or health consequences to ascertain the severity of abuse. The 44 who were questioned in more detail about alcohol use had an average of 5.1 alcohol-related illnesses per patient compared with 2.2 per patient in the 33 who were not questioned further ($P < .01$). Those questioned further were more likely to have diagnoses in the level 1 category as opposed to a level 2 or 3 category ($P < .01$; see Table 1). Only 34 of 77 patients (44%) had the word alcohol in any context listed on the problem list, and only 37 (48%) had alcohol mentioned in the discharge summary. Among those 77 patients identified with an alcohol-related illness, only 18 (23%) had a referral to either the detoxification ward, Alcoholics Anonymous, or the psychiatric consultation service. Referral was more likely for patients with level 1 diagnoses ($P < .05$). Thus, of the total population of 132 patients with an alcohol-related disease, only 44 (33%) had any in-depth history taken regarding alcohol abuse and only 18 (14%) were referred for counseling for their possible problem with alcohol.

After Intervention

During the second half of the study, 197 patients (89 women, 108 men) made up the study population (group II). Of the 197 patients, 131 (66.5%) had one or more alcohol-related diseases identified. Among the 131 patients, 54 women and 77 men had a group mean age of 45.7 years (SD, 15.8 years; range, 18 to 95). In all, 66 patients with a mean age of 49.2 (SD, 16.3 years) were admitted with disorders not considered related to alcohol abuse (see Table 2).

Of the 131 patients, 118 (90.1%) were asked by either a resident or intern about their consumption of alcohol. The mean age of these 118 patients questioned was 44.5 years (SD, 16.0) compared with 57.1 years (SD, 21.2) of those not questioned, which was significant ($P < .01$). The group questioned were more likely to have a level 1 diagnosis as opposed to level 2 or 3 ($P < .01$).

Of the 118 questioned, only 50 patients (42%) were asked more extensive questions to ascertain the severity of abuse, and they had an average of 3.9 alcohol-related disorders compared with 2.1 in the group who were not asked any further questions ($P < .01$). The group questioned in detail more often had level 1 diagnoses

($P < .01$). Of those 118 patients questioned about alcohol consumption, only 37 (31%) had alcohol mentioned in the discharge summary, and 48 (41%) listed alcohol on the problem list in the medical chart. Last, 31 patients (26%) had a referral to either a detoxification program, Alcoholics Anonymous, or were court ordered for evaluation and treatment.

Further analysis was done to assess whether there was improvement in the frequency with which diagnosis and interventions were done or offered during the second half of the study compared with the first. After attempts to raise the level of concern for alcoholism diagnosis and treatment as described, interns and residents questioned a greater percentage of patients with alcohol-related diseases about alcohol abuse (91% versus 58%; $P < .01$). In addition, the mean number of disorders needed to prompt a query regarding alcohol use was less in the second period ($P < .01$). Moreover, the physicians did refer a higher percentage of patients for treatment of their alcoholism (26.3% versus 13.6%; $P < .05$).

In both portions of the study, the age of patients was an important predictor of physicians' behavior. In general, younger patients were referred for treatment more often than older patients along the whole spectrum of ages ($P < .05$). Moreover, older patients were referred for follow-up for their alcoholism less frequently than younger patients, even if they had level 1 diagnoses. In all phases of the study, employment status, sex, and race were not statistically significant predictors for identification or referral for treatment options.

To investigate the independent effect that our proposed modifiers (age, sex, employment status, race, introduction of an awareness program, and the level of a patient's alcohol involvement based on the level of the alcohol-related disorder) have on residents' and interns' documentation of alcohol-related issues, we did a multivariate analysis using stepwise logistic regression analysis. Based on our previous univariate analyses, we entered only six variables that seemed to have a possible effect on increased awareness of alcohol-related illnesses. When the five adjustment factors (namely, level of alcohol disease, age, sex, employment status, and race) and the single experimental factor, before or after an alcohol disease awareness program, were entered into the model to predict increased documentation of alcohol diseases, only the three factors, level, age, and program, were independently significant factors for influencing awareness (Table 3).

TABLE 3.—*Results of Stepwise Logistic Regression*

Effect	Odds Ratio	95% Confidence Interval	P Value
Level	3.10	1.90-5.00	< .01
Age	0.67	0.05-0.90	.02
Program	2.08	1.06-4.00	.03

Discussion

Alcoholism imposes enormous financial and human costs to our society. A ten-year Kaiser-Permanente study showed that the heaviest drinkers had a mortality rate 100% higher than controls and documented the dire consequences associated with long-term ingestion.[23] Similarly, patients with alcoholism who relapse die at a rate 4.96 times that of an age-, sex-, and race-matched representative sample.[24] As in any disorder, appropriate therapeutic intervention depends on an appropriate diagnosis. Moreover, early diagnosis and treatment of alcohol abuse do improve the prognosis for recovery.[25-27] Many obstacles appear to prevent the diagnosis of alcohol abuse from being made, however.[28-30] These may include lack of physician awareness about the scope of alcohol-related disorders, physicians' punitive attitude regarding alcohol abuse, alcoholic patients' behavioral patterns, and subspecialization of medicine into disciplines that fail to encompass alcohol abuse as a specific area of interest. An example of the last problem was examined by a study at Johns Hopkins Hospital (Baltimore, Maryland) where identification rates by house staff of alcohol abuse ranged from 0% for gynecologists to 20% for surgeons to 66% for psychiatrists.[27]

Only a few studies have assessed the ability of house staff in teaching hospitals in the United States to adequately address the question of alcoholism. In one study, 300 patients admitted to a university hospital were screened with the MAST.[31] From this, 27 patients were identified with what was defined as a positive MAST score. Yet, only 10 of the 27 patients were asked by house staff about alcohol consumption. Moreover, only 9 of 27 patients were referred for the treatment of alcohol abuse despite suggestions for consultation by the investigator. In another study, alcohol use was assessed by house staff on an orthopedic service at a county hospital.[32] They used the CAGE screening interview to identify 27 patients with alcohol-related problems out of 87 consecutive admissions. The orthopedic service house staff identified alcoholism in only 3 of these 27 patients. A British study documented that only 36% of junior physicians questioned medical and surgical patients about alcohol intake.[33] Numerous other studies have found similarly low frequencies of alcohol abuse detection in the outpatient setting.[11,34-36] Further, even when alcoholism is identified, referral for treatment is infrequent.[37]

We had hypothesized that house staff on a general medical ward of a county teaching hospital would be much more likely to identify and treat patients for alcoholism compared with other disciplines' house staff, particularly because many of the patients were admitted with diseases that had a strong association with alcoholism. In this regard, it is astonishing that about 70% of patients admitted to the medical service of such a hospital have possibly alcohol-related medical problems. This is in stark contrast to the prevalence of 15% to 30% estimated in studies, notwithstanding that they used different standardized alcoholism screening instruments.[22] Furthermore, only 58% of the probable cases had chart

documentation by either a resident or intern regarding alcohol consumption. It is possible that more patients were asked, but the information was not recorded. More than 40% were not asked about alcohol use at all. Even if lack of documentation is the entire problem, it nonetheless reflects a different view of the risk factors of alcohol abuse compared with that for risk factors of other common disease states. These data do suggest that patients on a medical service with an alcohol-related illness are in general more likely to be asked about alcohol consumption than patients admitted throughout a general hospital.[32]

After our educational effort and emphasis on different intervention modalities, chart documentation regarding questions about alcohol intake improved to 90%. This suggests that a multifaceted approach to the identification and treatment of alcoholism is better than a single focused effort. It also shows that such an approach yields a high success rate.

Referral for the treatment of patients with alcoholism has also been less than ideal. Although 41% (855) of trauma patients admitted to a major trauma center over a 28-month period had alcohol present in their blood, there was no formal process for treatment referral of such patients.[6] A similar study from an emergency department showed that not one patient from a group who had been involved in a motor vehicle accident and had a detectable blood alcohol level was specifically referred for an evaluation of alcoholism.[38] In our study, 26% of patients with alcohol-related disease were referred for further treatment after the intervention, which did reflect an improvement over the 13% rate who were referred during the first half of the study. Because routine blood tests such as mean corpuscular volume, uric acid, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase levels lack sensitivity and positive predictive value when used individually for the detection of alcohol abuse,[39-42] we also used specific disease states as indicators of possible alcohol abuse. This may account for the more frequent treatment in those patients who had diseases commonly seen in patients with alcoholism. In fact, patients with disorders that were most likely to be alcohol related were most often referred. Unfortunately, for diagnoses that were less suggestive (levels 2 and 3), but also associated with alcoholism, there was no such improvement, suggesting that physicians tend to wait for the most serious sequelae before diagnosing alcoholism and referring patients for alcohol treatment.

It is also interesting that our house staff performed better in documenting and treating alcoholism if the patients were younger. Possibly the older patients with alcoholism are viewed as incorrigible; treatment interventions are therefore considered futile in these patients. Further, although male gender has been associated with a higher rate of identification of alcoholism by physicians,[43] our study did not find any effect of patients' sex on identification or treatment referral.

Therefore, education to raise physicians' and house staffs' level of consciousness regarding identifying and treating alcoholism is sorely needed. Although the MAST and CAGE questionnaires are efficacious and economical in identifying alcoholism,[44,45] their use is limited. Recently some new techniques for detecting alcoholism have been devised. When lifestyle risks were routinely assessed in a community hospital, physicians identified an unusually high frequency (90%) of alcoholism among patients they admitted.[46] The explanation offered is that physicians will address alcoholism more readily if it is viewed in the context of other familiar detrimental lifestyle risks such as smoking, high-cholesterol diets, and inadequate physical exercise. There are also data suggesting that physicians can improve their ability to estimate a patient's risk for an alcohol abuse disorder if likelihood ratios for CAGE scores are used. This allows physicians to stratify patients along a continuum of risk for abuse.[47] Also, a simple, short, routine inquiry protocol has recently been shown to be an effective method to identify and help this segment of the population.[48]

Our results provide evidence that the introduction of an awareness program can have an independent effect on physicians' behavior regarding the documentation of alcohol-related problems. Although this factor remains relevant even after adjusting for other well-known factors that prompt a physician to document alcohol problems, the most effective indicator to prompt physicians' action is previous documentation of serious alcohol-related illnesses (level 1). The presence of such documentation provides a 100% increased chance that a physician will encourage or refer a patient for subsequent alcohol-related treatment. Given the extraordinary prevalence and the enormous personal and economic consequences of alcoholism, better programs that focus not only on the diagnosis but also on intervention strategies for alcoholism and hazardous drinking are desperately needed. Although logical explanations have been offered as to why physicians seem loathe to intervene in this chronic illness,[49] what has been referred to as a "pernicious attitude of defeatism about alcoholism"[50] must be eradicated. Our study provides evidence that simple programs and continuous interventions can raise housestaff awareness of alcoholism as a chronic disease. It is critical that such programs and efforts be instituted in all teaching programs so that the next generation of physicians begins to deal effectively with this problem that exacts enormous costs from our society. Our study offers some hope that this is a realistic goal.

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Articles

Screening for Depression Among Newly Arrived Vietnamese Refugees in Primary Care Settings

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A brief, culture-specific, self-report screening measure for depression, the Vietnamese Depression Scale, was used to determine the prevalence of depressive symptoms among 1,998 consecutive adult Vietnamese refugees who presented at 10 public health clinics within 2 months of their arrival in the United States. Of these patients, 6% met the criterion for a probable case of depression ("positive"). Being divorced, separated, or widowed and poorly educated were strongly associated with a greater likelihood of screening positive. Somatic complaints were common and induced considerable anxiety about physical health status. Nearly a third of the patients reported sadness and dysphoria; culture-specific symptoms of depression also were prevalent. Our findings document the feasibility of screening for depression using the Vietnamese Depression Scale among Vietnamese refugees, particularly in primary care settings where they are first likely to be seen by health professionals after arrival in their host country.

(Buchwald D, Manson SM, Brenneman DL, et al: Screening for depression among newly arrived Vietnamese refugees in primary care settings. West J Med 1995; 163:341-345)

A great deal of interest has been shown recently in the detection and management of depression in primary care settings.[1-4] An estimated 54% of persons suffering from psychiatric disorders are seen only in the primary care or general medical sector.[5] Among patients with affective disorders, the Epidemiologic Catchment Area study showed that as many as 15% had sought help only in the general health care sector, with a similar number seeking help from mental health specialists.[6] Other reports indicate that almost half of all office visits to physicians in private practice that resulted in a primary or secondary diagnosis of a psychiatric disorder were to a nonpsychiatrist; 28% of these were for depression.[7]

Similar circumstances may be found among the more than 1 million Southeast Asian refugees who live in the United States (R. Johnson, International Rescue Committee, oral communication, June 1994). Specialized mental health services are in short supply, and it has long been recognized that the cultural stigma attached to mental illness in this population encourages seeking help in primary care settings.[8] Because most refugees are seen in public health clinics on entry into the United States and psychological distress may be greatest within the first year of arrival,[9-11] early screening for depression seems both feasible and warranted.

In this article we describe the use of a previously developed, culture-specific depression scale to examine the nature and extent of this phenomenon among adult Vietnamese refugees seen in primary health care clinics in four states within two months of their immigrating to the United States.

Patients and Methods

Patients

The patients were all ethnic Vietnamese refugees 16 years of age or older who had arrived in the United States in the previous two months and were seen at one of ten study sites. All patients completed the Vietnamese Depression Scale (VDS).[12]

Vietnamese Depression Scale

The VDS is an 18-item, culture-specific self-report instrument that can be completed in five minutes by any Vietnamese person with at least four years of formal education. It is administered orally by an interpreter to persons with less or no formal education. The VDS was

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developed using key informants and a known case-non-case–matched control design.[12] Because the presentation and symptoms of depression may be different across cultures and can be obscured by the use of measures developed for other populations, the VDS contains six culture-specific items associated with depression among the Vietnamese, as well as six questions each about physical and psychological symptoms. The derivation and meaning of these culture-specific symptoms have been previously described in detail.[12] In our initial work, a cutoff of 13 points on the VDS identified 91% of depressed patients and 96% of a community control sample.[12] Subsequently, its sensitivity has been validated in a primary care study that found that 89% of patients identified as depressed by the VDS were confirmed to have major depression on a psychiatric evaluation using a modified structured interview.[13] Other work among newly arrived Vietnamese refugees showed a sensitivity of 64%, a specificity of 98%, and positive and negative predictive values of 75% and 97%, respectively, using a semistructured interview administered by a native Vietnamese-speaking psychiatrist as the standard.[14]

Study Sites

A pilot project at the Multnomah County Refugee Health Clinic in Portland, Oregon, was prompted by inappropriate referrals to the Oregon Health Sciences University Indochinese Psychiatric Clinic and difficulties experienced by community health nurses in assessing the mental health of refugee clients. Six months after its initiation, the Centers for Disease Control and Prevention (Atlanta, Georgia) supported the extension of the pilot project to nine additional sites. The ten refugee health clinics that participated in this study included four in Washington (Seattle, Olympia, Spokane, and Yakima), three in Oregon (Portland, Salem, and Hillsboro), two in California (San Jose and San Diego), and one in Hawaii (Honolulu). At least one Vietnamese ancillary health professional was employed at each site.

Methods

Two of us (S.M.M. and N.G.D.) traveled to each clinic to conduct half-day orientation and training sessions. These sessions reviewed scale development, the protocol for administering and scoring the scale, pilot study findings, intake logistics, referral procedures, and forwarding of the data for statistical analysis. An audiotape in the native language developed by a Vietnamese colleague explained these same matters and described the nuances of each scale item at greater length. Oregon Health Sciences University staff were available for telephone consultation. Quarterly statistical reports were generated for individual clinics as well as the aggregate.

After staff orientation and training, the VDS was incorporated into the clinic intake procedure, which also elicited information on sociodemographic background, medical history, and reason(s) for the visit. Community health nurses reviewed this information, scored the VDS, and called the results to the attention of the treating physician, who determined the need and appropriateness of a referral for mental health services.

The length of clinic involvement ranged from 14 to 18 months. Although several factors affected the duration of involvement in the screening project, the primary one was a loss of program funds with corresponding staff reductions. The comprehensiveness of the screening effort was checked at least once at each site by comparing the number of scales administered during a randomly selected month to the clinic's report of the number of adult Vietnamese refugee patients seen during the same month. No clinic evidenced less than 96% completeness in VDS screening.

Statistical Analyses

Percentages were compared using the χ^2 statistic. Student's t tests were used to detect differences in continuous variables. In the univariate and multivariate logistic regression analyses, screening positive for depression—that is, a score of ≥13—was used as the dependent variable and demographic factors as independent variables. Internal consistency was examined using Cronbach's α coefficients; because the scale is not the same for each item in the VDS, an adjusted α also was calculated. α Coefficients were determined for the entire sample, as well as for subgroups identified by gender and educational level. Because multiple tests were done, only those with P values of .01 or less were considered statistically significant.

Results

During the study period, 1,998 adult Vietnamese refugee patients were screened within two months of their arriving in the United States. Four of the ten clinics contributed 90% of these persons. This disparity in enrollment reflected differences in the relative size of the refugee populations residing in the catchment areas. The average VDS score for all patients was 3.19 (standard deviation ± 4.75); 115 (6%) scored at or above the threshold criterion of 13. As shown in Table 1, the average age of the patients was 31 years (range, 16 to 85), 59% were male, and more than half of the patients were single. Two thirds had received some secondary level education, but almost a quarter had six years or less of formal schooling.

Table 1 also shows important variations in scale scores by patient characteristics. Significantly more women than men met the threshold criterion (7% versus 5%; $P < .005$). Likewise, the number of persons who met the criterion was disproportionate among older patients, particularly those older than 40 years ($P < .005$). Univariate analyses confirmed that persons scoring at or above the threshold were significantly older than those who score below (mean age, 33.9 versus 30.4 years; $P < .001$). Persons with scores of 13 or higher also distributed unequally across the single (4%), married (5%), and other (17%) categories (which included people who were divorced, separated, or widowed), with far more than expected among the last group ($P < .001$). In

TABLE 1.—*Patient Characteristics and Scores on Vietnamese Depression Scale (VDS) (n = 1,998)*

Potient Chorocteristics	VDS Score <13, n =1,883 No. (% row) [% column]	VDS Score ≥13, n = 115 No. (% row) [% column]	Totol No. (% row)
Mean age, yr*	30.4	33.9†	31
Age, yr*			
<21.....	365 (20) [96]	16 (14) [4]	381 (19)
21-30.....	754 (41) [96]	35 (31) [4]	789 (40)
31-40.....	415 (22) [95]	24 (21) [5]	439 (22)
41-50.....	213 (11) [89]	26 (23) [11]‡	239 (12)
51-60.....	80 (4) [90]	9 (8) [10]	89 (5)
≥61.....	34 (2) [92]	3 (3) [8]	37 (2)
Sex*			
Male.....	1,131 (60) [95]	55 (48) [5]	1,186 (59)
Female....	746 (40) [93]	60 (52) [7]§	806 (41)
Marital status*			
Single.....	935 (54) [96]	42 (43) [4]	977 (53)
Married ...	738 (42) [95]	42 (43) [5]	780 (43)
Other.....	67 (4) [83]	14 (14) [17]‡	81 (4)
Education*			
Mean years	9.6	8.4§	9.5
Highest grade			
None	19 (1) [79]	5 (5) [21]‡	24 (1)
1-4	92 (5) [91]	9 (8) [9]	101 (5)
5-6	297 (16) [92]	25 (24) [8]	322 (17)
7-12	1,217 (68) [95]	61 (57) [5]	1,278 (67)
≥13.....	177 (10) [97]	6 (6) [3]	183 (10)

*Information on some patients is missing.
†$P < .05$. ‡$P < .001$. §$P < .01$.

addition, a lack of formal education was associated with a significantly higher percentage of persons reaching the threshold score: 5 (21%) of those with no education, 9 (9%) completing first to fourth grades, and 25 (8%) with a fifth- to sixth-grade education met the criterion compared with 61 (5%) persons with secondary level education and 6 (3%) with college experience ($P < .001$). Last, patients with VDS scores of 13 or higher had resided longer in the United States than those not classified as depressed (0.79 months versus 0.87 months; $P < .05$), a finding of unlikely clinical importance. Univariate logistic regression models using these same demographic variables confirmed these findings. When these variables were entered into the model simultaneously, however, thereby adjusting their relationship with VDS scores for the confounding effects of other variables in the model, only being separated, widowed, or divorced ($P = .008$) and level of education ($P = .01$) were significant predictors.

As seen in Table 2, the frequency and level of physical symptom endorsement also revealed several interesting patterns. Overall, headaches were reported by 414 (21%) persons, backaches by 253 (13%), and limb aches by 240 (12%). Altogether, 26% of patients reported being anxious about one of these symptoms. In addition, 20% experienced loss of appetite and physical fatigue. For each physical symptom, the prevalence was significantly higher in the depressed than the nondepressed group (data not shown, $P \leq .001$).

Dysphoria was the most frequently reported psychological symptom, having been experienced by 610 persons (31%). Difficulty in concentrating was almost as common, with 597 (30%) patients indicating that they often or always had this problem. Other symptoms of depression—notably downhearted and low-spirited, low-spirited and bored, exhausted, and feeling hopeless—were described as present by about 10% of the sample. Again, patients who met the threshold criterion reported a significantly greater presence of all psychological symptoms than those who did not meet the criterion (data not shown, $P \leq .001$).

Finally, culture-specific symptoms also were frequent. For example, 321 (16%) patients were sad and bothered, and 199 (10%) were bothered. Anger, shameful and dishonored, and desperation were expressed by about 7% each, and 65 (3%) patients often or always had the feeling that they were going crazy. Compared with those scoring less than 13, all culture-specific symptoms were more common in the depressed group (data not shown, $P \leq .001$).

The reliability of the VDS in this population and setting was adequate. α Coefficients were calculated for the entire sample and by sex and educational level. Overall, the standardized α was .89; for gender and educational level, it ranged from .87 to .91.

Discussion

Several community-based surveys among Vietnamese refugees have found substantial and continuous physical and mental dysfunction following migration, related to

TABLE 2.—*Prevalence of Individual Symptoms in Vietnamese Patients, (n = 1,998)*

Type of Symptom	Potients, No. (%)
Physical symptoms	
Headaches	414 (21)
Backaches	253 (13)
Limb aches	240 (12)
Anxiety about above symptoms	504 (25)
Loss of appetite	391 (20)
Fatigue	382 (19)
Psychological symptoms	
Sad	610 (31)
Difficulty concentrating	597 (30)
Exhausted	231 (12)
Downhearted and low-spirited	219 (11)
Low-spirited and bored	162 (8)
Hopeless	137 (7)
Culture-specific symptoms	
Sad and bothered	321 (16)
Bothered	199 (10)
Angry	133 (7)
Shameful and dishonored	138 (7)
Desperate	112 (6)
Going crazy	65 (3)

instability in work, finances, spouse relations, lifestyle, traumatic experiences, and duration of residence in the host country.[15-18] For example, in one study Southeast Asian refugees at highest risk for clinically important psychological distress were found to be the least educated and English-proficient, the most dependent on welfare, the poorest and most frequently unemployed, older and widowed, and those with the most traumatic migration histories.[9] In a more recent survey in which a structured clinical interview was administered to 201 newly arrived Vietnamese refugees, war veterans and married persons were substantially more likely to have a psychiatric disorder.[11] Of interest, the rate of major depression (5.5%) reported by the investigators is remarkably similar to the 6% of patients in our study who had VDS scores suggestive of depression (≥13). A similar prevalence of VDS scores of 13 or higher was observed in a group of young adults screened in a refugee camp.[19]

More selected samples from primary care facilities also have been the subject of investigation. The screening of Southeast Asian refugees using standardized instruments revealed that almost two thirds had scores suggestive of depression.[20,21] Among Vietnamese, the VDS was used to assess the prevalence of depression among 97 patients in a community health clinic.[13] Depression was detected in more than half, yet most cases had not been diagnosed by the primary care physician, perhaps because virtually all patients presented with physical complaints. At the Khao I Dang refugee camp in Thailand, a third of all unselected patients examined by a psychiatrist received a psychiatric diagnosis compared with 2% of those examined by a general physician during the same interval.[22] Though not exclusively concerned with depression, this last report further underscores the frequency with which mental health problems escape detection even by trained health care professionals working with Southeast Asian refugees at highest risk.

Last and not surprising, at least half of Southeast Asian refugee patients seen at special psychiatric clinics met criteria for major depression and anxiety.[23-27] Widowhood and traumatic experiences were correlated with more symptoms. Of particular interest, a review of Vietnamese patient records from two Los Angeles County mental health centers produced similar results[28] and reconfirmed the predominance of somatic complaints among Southeast Asians.[24,28] Again, traumatic experiences, isolation, or estrangement from family were closely associated with the presence of depression. Even more important, 87% of all patients either rejected or prematurely terminated treatment.[28]

The results of the current study are congruent with this body of knowledge. Specifically, the multivariate analysis excluded sex, age, and duration of residence as predictors of depressive symptoms, yielding marital status and educational level as the most salient factors. Moreover, as emphasized in previous investigations, Southeast Asian patients frequently somatize their depression, presenting with apparently physical complaints that may be mistakenly accepted as such by their physician.[29] Our results can be seen as consistent with this observation, although there was no systematic attempt to attribute symptoms to medical or psychological causes. Vietnamese refugees also are able to describe their distress in relatively sophisticated psychological terms. The meaning of some of these terms overlap with those used by non-Vietnamese providers; others do not. Hence, the communication problems—and real differences in symptom presentation—that may occur across such cultural boundaries diminish the likelihood of depression being detected among this population.

A discrepancy between our results and much of the existent literature is the relatively low prevalence of probable depression. This finding can be understood in several ways. First, although only 6% of our patients had VDS scores of 13 or higher, 31% reported a dysphoric mood during the past week. Dysphoria is a central feature of depression; yet, it is a necessary but insufficient condition for the disorder. Second, the specificity of the VDS as a screener for depression may be greater than its English counterparts, perhaps due in part to the careful attention given to culturally specific symptoms. Third, although recruited through primary care settings, study participants actually approximated the population of all adult Vietnamese refugees entering the United States through these ten geographic areas during the study period. Pressure from sponsors, volunteer agencies, public health services, and the Immigration and Naturalization Service to submit to health screening soon after arrival virtually guaranteed their visit to the clinics in question. Indeed, most patients had no special medical needs that would motivate their return to the clinic after the initial visit. Thus, the dynamics of seeking help that characterize other primary care patient groups may not have been at work in the same way with this one. Finally, the relatively low prevalence of probable depression may be due to the correspondence of the screening period with the euphoria or brief "honeymoon" period refugees may experience shortly after immigration.[9,11,15,30,31]

In conclusion, the primary medical care setting is a highly appropriate focus for detecting depression among Southeast Asians. This study demonstrates the feasibility of screening with the VDS for such problems in Vietnamese refugee patients. Multiple somatic symptoms coupled with any indication of depressed mood should alert clinicians to the possible presence of an affective disorder. Primary care patients already have come for help and accepted the "patient" role; therefore, psychiatric case finding and offering treatment may be less intrusive than it would be in other settings. Furthermore, because this setting is not defined as "psychiatric," the stigma associated with mental health treatment may be more easily minimized, especially for populations similar to the one considered in this article. Primary care professionals should consider incorporating the VDS into the clinical assessment of Vietnamese patients seen in general medical practices.

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Articles

Role of Previous Claims and Specialty on the Effectiveness of Risk-Management Education for Office-Based Physicians

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We analyzed the medical malpractice claims data of 1,903 physicians between 1981 and 1990 to assess the efficacy—a reduced incidence of future claims and decreased payout in the event of a claim—of risk-management education for office-based physicians. Physicians were participants in the Oregon Medical Association's medical liability program and represented all recognized specialties and all geographic areas of the state. Each physician's claim and payout history before and after 4 sequential risk-management education programs was entered into a random-effects probit model that allowed for a longitudinal rather than a cross-sectional analysis. For most physicians, there was increased claim vulnerability following 1 or 2 risk-management education courses but decreased vulnerability after additional courses. Among all physicians, having a previous claim substantially increased the risk for a future claim. Risk for an additional claim doubled (from 7% to 14%) for physicians who had a claim in the previous year. Of all specialists who have had claims, anesthesiologists (reduction in claims incidence from 18.8% to 9.1% and in payout from 14.6% to 5%) and obstetrician-gynecologists (reduction in claims incidence from 23.3% to 15.2% and in payout from 11.6% to 4.2%) benefit most from cumulative risk-management education.

(Frisch PR, Charles SC, Gibbons RD, Hedeker D: Role of previous claims and specialty on the effectiveness of risk-management education for office-based physicians. West J Med 1995; 163:346-350)

The role that physicians play in the generation of medical malpractice claims is a subject of continuous debate. Why do some physicians experience one or more claims during their careers and other physicians have none?

The central question is whether or not identifiable aspects of office-based practice are associated with increased vulnerability to claims. For example, physician characteristics such as surgical specialty,[1-3] male sex,[1] and years in practice associated with increasing age[3] all have been linked with an increased risk of claims. A history of a previous claim also has been associated with having future claims.[1,4,5] Whether this last association can be attributed to deficiencies in practice, underlying and unobservable physician characteristics, or some other factor is unclear.

The presumption among risk managers, however, is that certain controllable events in practice render a physician more or less vulnerable to malpractice claims. For more than a generation, risk-management education (RME) courses have focused on such events in physicians' practices. Often sponsored by insurers, RME teaches physicians how to exert control over their practices and avoid incidents that cause injuries to patients and trains physicians to be better defendants in the event of a claim.[6] Risk-management education courses are increasingly based on a review of closed claims and, as such, are increasingly specialty-specific. Although RME enjoys considerable economic and legislative support, its influence on preventing claims has not been studied extensively.[6-9] A reduction in the incidence of hospital-based claims associated with in-house risk management and quality assurance programs has been shown,[10] but studies have not been done of the effectiveness of RME programs on office-based practitioners.

To assess the efficacy of RME for office-based physicians in reduced claims incidence and decreased payout in the event of a claim, our group applied a statistical model described previously[11] and that differs from those used by other medical malpractice researchers.[4,12-14] The analysis was based on available claims histories for physicians over a ten-year period and on the amount of payout for each claim. Using longitudinal data, we were able to estimate static effects (specialty and sex) and

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dynamic effects (those that change over time such as age, previous claim history, and RME courses), illuminating the influence and relative strength of some dynamic factors on vulnerability to claims rather than examining the issue over a fixed time interval, as in cross-sectional studies.

Data Set

The study sample consisted of 1,903 physicians representing 16,083 practice years insured under the Oregon Medical Association's malpractice liability insurance program between 1981 and 1990. All recognized specialties and all geographic areas in the state were represented.

Information on each subject was obtained from several databases from the medical society. A malpractice claims database provided each physician's claims history, disposition (closed with payment, closed without payment, and open), and the amount of any award or settlement. The membership database provided age, sex, specialty, and dates of attendance at four sequential RME courses (described in Figure 1) developed and offered by the state medical society.

Only written demands for money or services were counted as claims. The date of the claim used in this study is the date of the alleged injury, which bears a direct relationship to the usefulness of RME intervention. This definition is distinguished from the date the claim was reported to the insurance carrier or when a suit was filed.

Statistical Methods

The Oregon data (1981 to 1990) on medical malpractice claims was analyzed using a random-effects probit model.[11] The model estimates vulnerability to a medical malpractice claim in each practice year for each physician conditional on a mixture of time-varying and time-invariant covariates. In this application, time-invariant covariates were physician's sex and specialty (surgical versus nonsurgical). Time-varying covariates were age, the number of RME courses taken by physician i to year k, and previous claim history. In addition, the model incorporates a random effect of "claim vulnerability," assumed to be normally distributed in the population of physicians. This random effect represents unobservable or unmeasured characteristics that place one physician at a greater risk for experiencing a malpractice claim than another physician. In addition, we determined whether the effects of RME on claim vulnerability differ before and after a physician's first malpractice claim. More detailed discussion of the strengths and weaknesses of the random-effects probit model are provided elsewhere, including a discussion of robustness to violations of assumptions.[11]

In the past, Poisson process models have been used to analyze claims incidence data.[4,12-14] Using Poisson process models, however, we could have examined only the relationship between the total amount of RME courses and the total number of claims for the entire

Risk-Management Education Course Description

Workshop Series One: 1979-1981

All participants during this period attended the same workshop, the purpose of which was to develop statewide a common medicolegal lexicon and an understanding of the state's medical malpractice statutes and case law. Particular emphasis was placed on the process of obtaining informed consent, the importance of not inappropriately altering medical records, and how to report and respond to malpractice claims.

Workshop Series Two: 1982-1984

The medical society created on videotape and introduced a series of vignettes to illustrate key nonclinical communications concerns that frequently turned unexpectedly bad outcomes into claims. The medicolegal lexicon, case law, and claims handling segments were updated.

Workshop Series Three: 1985-1987

For the first time, the society bifurcated its RME programs. Those who attended the first and second series received advanced training building on the second series program segments. Physicians new to the sponsored liability insurance program received an updated, though simplified, version. Most important, the society offered specialty-specific versions of the advanced workshop to obstetrician-gynecologists, family physicians doing obstetrics, and anesthesiologists, all under the joint sponsorship of the respective state specialty societies.

Workshop Series Four: 1988-1990

At this point, two distinct programs emerged. "Basic Training in Malpractice Loss Prevention" became the society's entry-level RME course. It encompassed updates of the segments discussed in the previous series of programs. An advanced course, "From the Exam Room to the Courtroom," taught physicians to assist effectively in the defense of their claims. Updates on state statutory and case law and current claims trends were included. Specialty-specific versions of the advanced course were offered to anesthesiologists, family physicians, general surgeons, orthopedists, radiologists, and pathologists.

Also during this period, all physicians and hospitals involved in obstetrics agreed to the use of a Uniform Prenatal Form to document patient care. In addition, anesthesiologists who follow their national specialty society's intraoperative monitoring guidelines received substantial premium discounts, in the form of reductions in rate classification, signifying a corresponding decrease in risk exposure.

Figure 1.—The risk-management education (RME) courses developed by the Oregon Medical Association's Loss Prevention Education Program are described.

study period, regardless of whether or not RME preceded a claim. The model used in the analysis of these longitudinal data examines the effects of measured and unmeasured physician characteristics on the probability of a claim in each practice year. Claim propensity is allowed to vary randomly from physician to physician. Because we focus on the probability of a claim in each individual year and not the rate over the entire period, we can directly examine the effects of physician characteristics that vary from year to year—the effect of having a claim in the previous year on the probability of having a claim in the current year. Perhaps of greatest importance in this article is determining the effect of RME courses taken before year t on claim propensity in year t. In this way, we compare claim proneness before and after RME in the same physician.

Results

Efficacy of Risk-Management Education

Applying the final statistical model to ten years of malpractice claims data shows that efficacy—decreased vulnerability to claim and decreased payout—of RME is related primarily to previous claims history and to specialty.

The effects of RME are both linear ($P < .01$) and quadratic ($P < .01$), with claims vulnerability following one or two courses increasing for most physicians but decreasing with additional courses.

Risk-Management Education and Previous Claims Experience

A significant age-by-RME interaction was observed in the earlier models, indicating that as physicians age, they benefit more from RME than when they were younger ($P < .01$). When a history of a previous claim and the quadratic effects of age and RME were added to the statistical model, the RME-by-age interaction was no longer significant, but RME by previous claim remained statistically significant ($P < .01$). Cumulative RME, therefore, was associated with lower vulnerability and fewer payouts significantly more often for physicians who had a previous claim than for those who had never had a claim, regardless of age.

Claims Vulnerability and Specialty

The surgical and nonsurgical specialties were further subdivided into eight categories and added to the model (Table 1). Differences between specialties were significant ($P < .01$).

For those physicians who have never had a claim, cumulative RME has a limited, even adverse, effect. In contrast, the cumulative effect of RME on those physicians with previous claims remains beneficial in terms of decreased vulnerability to claims and decreased payout ($P < .01$).

Anesthesiologists have an increased vulnerability to claims after two or more courses but decreased payout if a physician has had no previous claims. Once a physician has incurred a claim, cumulative RME is associated with dramatic decreases in claim vulnerability and payout.

Among obstetrician-gynecologists who have never had a claim, cumulative RME is associated with increased vulnerability and payout. Following a claim, however, cumulative RME is associated with a decrease in vulnerability and payout almost as dramatic as that noted among anesthesiologists.

Surgeons have a profile somewhat similar to anesthesiologists and obstetrician-gynecologists but to a less dramatic degree. Special surgeons show a unique pattern among the specialties. Risk-management education, regardless of previous claims history, appears to decrease payout despite a persistent increased vulnerability to claims.

TABLE 1.—*Observed Yearly Claim and Payout Incidence Per Specialty, Influenced by Number of Risk-Management Education (RME) Courses and History of Previous Claims (Yearly Percentage Risk to a Physician)*

		Before 1st Claim		After 1st Claim	
*Specialty**	*RME Courses*	*All Claims*	*Payout*	*All Claims*	*Payout*
Anesthesiology	0	9.2	2.9	18.8	14.6
	1	8.0	4.5	7.0	4.7
	>2	12.3	1.5	9.1	5.0
Radiology	0	7.6	1.7	9.3	0.4
	1	12.0	3.3	7.1	2.7
	>2	5.9	1.5	5.8	1.4
Obstetrics	0	11.5	3.5	23.3	11.6
	1	17.8	7.4	19.8	7.0
	>2	13.5	8.1	15.2	4.2
Primary care	0	5.1	1.5	8.9	3.1
	1	5.4	2.2	9.2	3.6
	>2	5.5	1.4	5.7	1.5
Medical	0	3.3	0.8	6.7	1.1
	1	6.4	1.0	7.4	1.6
	>2	3.6	0.8	4.5	1.7
Surgery	0	6.4	1.1	14.0	4.1
	1	11.4	4.4	15.0	4.2
	>2	7.8	2.3	8.9	2.5
Special surgery	0	9.5	3.1	13.8	5.9
	1	10.9	4.8	20.2	5.2
	>2	13.1	1.6	15.7	3.7
Other†	0	1.8	0.5	8.3	1.4
	1	5.7	3.1	6.1	1.5
	>2	4.2	0.0	3.1	1.6

*Specialties were taken from the medical society's specialty designations listing and grouped for risk exposure purposes as follows: *Anesthesiology*: anesthesiology and obstetrical anesthesiology; *Radiology*: diagnostic radiology, therapeutic radiology, and ultrasonography; *Obstetrics*: obstetrics, obstetrics-gynecology; *Primary care*: family practice, general practice, internal medicine, and pediatrics; *Medical*: allergy, addictionology, allergy and immunology, cardiology, critical care medicine, cardiovascular disease, dermatology, diabetes, endocrinology, epilepsy, gastroenterology, medical genetics, infectious diseases, immunology, maternal-fetal medicine, neurology, nephrology, oncology, pulmonary disease, reproductive endocrinology, rheumatology, and vascular medicine; *Surgery*: colon and rectal surgery, emergency medicine, gynecology, maxillofacial surgery, ophthalmology, oral surgery, otolaryngology, pediatric surgery, plastic surgery, proctology, surgery, urology; *Special surgery*: cardiac surgery, neurologic surgery, orthopedic surgery, orthopedics, sports medicine, thoracic surgery, vascular surgery; *Other*: alcohol or chemical dependence, biochemistry, child development, child psychiatry, clinical pathology, dermatopathology, geriatrics, hematology, hospital administration, hyperbaric medicine, legal medicine, clinical nutrition, occupational medicine, pathology, pediatrics, pharmacology, physical medicine and rehabilitation, preventive medicine, psychiatry, psychoanalysis, psychosomatic medicine, and public health.

†Relative to "Other" specialties, all but medical subspecialties showed significant differences at $P < .001$ or less.

For primary care physicians who have never had a claim, RME minimally affects claims vulnerability or payout. After sustaining a claim, both are positively influenced. Medical specialists appear similar to primary care practitioners, except that they show a slight increase in payout when they have had both a previous claim and increased RME.

Among radiologists, RME contributes to some decreased vulnerability to claims in those with or without a previous claim. Risk-management education, however, appears to have little effect or even an adverse effect on payout.

Among all other specialties, RME is associated with an increased vulnerability to claims if a physician has no previous claims history and a decreased vulnerability to claims if the physician has a previous history of claims. Risk-management education appears to have little effect on payout.

Other Factors Contributing to Vulnerability to Claims

Surgical specialty ($P < .01$) and male sex ($P < .01$) contribute significantly to whether or not a physician has a claim.

Age is significantly correlated with a vulnerability to claims, and the correlation of age to vulnerability increases with advancing age ($P < .01$). The effect of age is quadratic; that is, the observed incidence of claims trends upward and then tapers off so that the incidence of claims is highest between the ages of 40 and 60.

A history of previous claims among all physicians of all ages and specialties significantly increased the risk for future claims ($P < .01$). The risk for an additional claim doubled, from 7% to 14%, for physicians who had a claim in the preceding year.

In addition, there is a significant random physician effect or heterogeneity ($P < .01$). This means that a vulnerability to claims is at least partially attributable to individual physician characteristics not measured and, perhaps, not observable.

Discussion

At first glance, RME for office-based physicians appears to be more detrimental than helpful. That is, the more RME physicians receive, the more vulnerable they are to future claims.

We do not know why RME fails to benefit most physicians who have never had a claim or why it may even increase their risk for future claims. Physicians who have never had a claim may use the psychological defense mechanisms of denial, rationalization, or both to protect them from feeling vulnerable to a claim. This means that they would either be able to remain unaware of the possibility of a claim or have a "good reason" why they are not vulnerable to a claim. In practice, therefore, such physicians would dismiss the possible malfunctioning of anesthetic equipment as an impossibility or think, "I have good relationships with my patients, so I don't need to worry about malpractice claims." Such psychological maneuvering, while largely unconscious and minimizing anxiety, may simultaneously "demotivate" the physician and remove any interest in or felt need for RME education. In this instance, the physician is also effectively impervious to educational interventions and therefore inhibited from introducing changes into practice.

Conversely, the structure and content of the RME courses may be at fault. As noted, courses were initially general in nature and predominantly nonclinical; only later courses were targeted to specialty-specific clinical problems (see Figure 1).

Nonetheless, the beneficial effects of RME for most specialists emerge after a claim occurs. We hypothesize that the emotionally disturbing and intensely human event of having a claim brought renders physicians more amenable to introducing changes into their practice than if they have not experienced a claim. In addition, the undeniable and sobering experience of litigation impresses on physicians the importance of risk-management strategies in preparing a defense of their case.

Beneficial Effects of Risk-Management Education

Risk-management education appears more beneficial in decreasing vulnerability to claims and decreasing payout for some specialists than for others. Anesthesiologists appear to benefit most from RME. This may be a function of the risk-management strategies specific to the specialty, such as the American Society of Anesthesiologists' intraoperative guidelines, which largely involve the use and maintenance of specific types of equipment.[15] Risk-management education for obstetricians and gynecologists, another group that appears to benefit from instruction, also involves specific indicators, checklists, and procedures, such as the Oregon Uniform Prenatal Form, in given clinical situations. Checklists and procedural forms may involve more concrete "things to do" than attempting to change a range of less easily identifiable and controllable behaviors, such as personal attitudes and the range of interactions that occur between physicians and their many patients.

Of particular interest are physicians who practice special surgery. Cumulative RME is associated with decreased payout if claims occur but does not result in measurable decreased claim vulnerability. This suggests that RME enables them to be "good" defendants; that is, they have good records, have had good communication with staff and patients, and have implemented effective office procedures, all of which make these physicians easier to defend. Nonetheless, special surgeons remain vulnerable to claims because their work is predominantly high risk, often with severely ill or injured patients.[3]

Timing of Risk-Management Education

A particularly disturbing finding is that physicians who experience a claim are twice as likely as those who do not to have an additional claim in the next 12 months. It may be that a personal event not directly related to

clinical medicine, such as marital discord, a breakup of a practice, or some similar stress-producing event, renders a physician "at risk" during the period before and after the critical claim incident. It is also possible that the event that led to a claim was itself so psychologically disturbing that it induced physical and psychological disequilibrium and may have jeopardized the physician's ability to practice optimally during the period following the event. There is considerable research and anecdotal data to support this last hypothesis.[16,17] An unpublished review of claims data over a ten-year period underscores our findings (T. Passineau, Physicians Insurance Company of Michigan [PICOM], unpublished data, June 1994). The author noted that the risk for a subsequent claim increases for a physician within 12 months, especially during the first 6 months immediately following a claim.

These findings also suggest that RME might be more effective for physicians if educational interventions can be accomplished within the year immediately following a claim, preferably within the first six months. This would also be an advantageous time to offer social support and similar strategies to diminish the emotional and physical repercussions of litigation.

Future Claims Trends and Risk-Management Education

In this study, surgical specialty is the most significant predictor of claim vulnerability, consistent with the view that surgeons in hospitals are more vulnerable to claims than their nonsurgical colleagues. Our study, however, tracks claims trends during a decade when procedures were predominantly done in hospitals by surgeons. The most recent claim trends suggest a shift to more claims arising in outpatient settings, in addition to hospital-based surgery claims, against primary care physicians that allege failure to diagnose cancers and heart disease as well as medication-related errors.[18] Furthermore, as health care reform efforts place greater emphasis on primary physicians as gatekeepers, the vulnerability of surgical specialists may be displaced to primary care physicians. Although not yet subjected to statistical analysis, the shift in settings may alert risk-management educators to track these trends carefully and update their activities accordingly because there are fewer beneficial effects of RME for primary care physicians than for the more procedurally oriented specialists. Updating might include identifying and developing risk-management activities that enable primary care physicians to "do" things such as following up on missed or canceled appointments or referrals, documenting telephone calls from and to patients, and instituting office processes and procedures to track prescribed and refilled medications.

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Conferences and Reviews

Common Injuries of the Shoulder
Diagnosis and Treatment

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Shoulder pain is often the presenting complaint of patients seeing their primary care physicians. Overuse and traumatic injuries make up most of the causes. A physical examination with minimal diagnostic tests can lead to the correct diagnosis in most cases. Most conditions can be treated conservatively (nonsurgically). Appropriate referral to a specialist depends on the severity of the initial injury or the patient's lack of response to conservative treatment (or both). We discuss common injuries of the shoulder, emphasizing a practical diagnostic and therapeutic approach.

(Donovan PJ, Paulos LE: Common injuries of the shoulder—Diagnosis and treatment. West J Med 1995; 163:351-359)

Patients commonly present to their primary care physician chiefly for shoulder pain. Most shoulder problems are due to overuse (tendinitis, bursitis) and trauma, and frequently there is an element of both these basic causes.

Acute shoulder injuries are not difficult to diagnose but require a basic understanding of shoulder anatomy and mechanics. A proper diagnosis is important to prevent long-term and permanent shoulder disability. Most shoulder conditions can be treated nonsurgically and thus are within the scope of practice for primary care physicians. In this article we discuss common overuse and traumatic injuries to the shoulder in adults, with emphasis on a practical diagnostic and therapeutic approach.*

Anatomic Considerations

The shoulder girdle comprises four bony articulations, the glenohumeral joint, the acromioclavicular joint, the sternoclavicular joint, and the scapulothoracic articulation. These osseous structures combine with the soft tissues of the rotator cuff muscles, scapular muscles, fibrous capsule, glenohumeral ligaments, and glenoid labrum to provide a stable but flexible unit that allows the widest range of movement of any joint in the body (Figures 1 and 2).[1]

The rotator cuff is derived from a specialized muscle group arising from the scapula and comprises the supraspinatus, infraspinatus, teres minor, and subscapularis tendons. These tendons insert around the head of the humerus, with the supraspinatus, infraspinatus, and teres minor tendons attaching to the greater tuberosity and the subscapularis tendon to the lesser tuberosity. In general, they act as humeral head stabilizers. The supraspinatus and the infraspinatus muscles are responsible for abduction and external rotation, respectively. The teres minor and the subscapularis are responsible for external and internal rotation, respectively. Tears of the rotator cuff muscles are often responsible for chronic disability of the shoulder and frequently go undetected in the evaluation of shoulder disorders.

The glenohumeral articulation is a ball-and-socket joint. The humeral head has a rather large articular surface compared with that of the glenoid. It is surrounded by a redundant capsule, allowing a wide range of motion. Mobility is obtained at the expense of stability, predisposing the joint to dislocation. The glenoid articulation is deepened by a rim of cartilage, the glenoid labrum, which is sometimes injured in shoulder dislocations or subluxations. The upper portion of the glenoid labrum is continuous with the tendon of the long head of the biceps muscle. Biceps tendinitis or injury to the long head of the biceps tendon is common in overuse and traumatic injuries of the shoulder.

The acromioclavicular joint is a plane joint whose structural integrity is derived from the acromioclavicular ligaments and intrinsic capsule. This joint has minimal mobility. Because of its prominence in the shoulder, it is often the site of injury and subject to degenerative changes (osteolysis, osteoarthrosis) with repetitive trauma. The clavicle is further stabilized by the coracoclavicular ligaments and can be damaged with severe acromioclavicular trauma. Coracoacromial ligaments form a superior shelf of the glenohumeral joint. This shelf, also known as the coracoacromial arch, has importance in the shoulder impingement syndrome.

The sternoclavicular joint is a relatively mobile saddle joint that is rarely the site of injury or disease. When

*See also the editorial by F. Cuomo, MD, "The Value of the History and Physical for Shoulder Pain," on pages 389-390 of this issue.

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ABBREVIATIONS USED IN TEXT

AP = anteroposterior
CT = computed tomography
MRI = magnetic resonance imaging
NSAIDs = nonsteroidal anti-inflammatory drugs
ROM = range of motion

injured, however, associated trauma to the surrounding vital structures—trachea, esophagus, and large blood vessels—should be considered.

Last, the scapulothoracic articulation is the sole link between the upper extremity and axial skeleton and functions as a platform from which the upper limb operates. It is susceptible to both direct trauma with associated injury to the chest wall and underlying vital structures and indirect injury by traction through the musculotendinous structures.

Bursal structures around the shoulder allow smooth gliding motions to take place between muscle groups and bony structures. Often the large subdeltoid and subacromial bursae are involved, with clinical symptoms caused by overuse or injury. With recurrent inflammation, thickening of the bursal walls, with or without calcific deposits, may develop.

Types of Injuries

Overuse

Overuse injuries of the shoulder include bursitis, tendinitis (rotator cuff, biceps tendon, or both), and degenerative or post-traumatic arthritis.[2] The elements of overuse that are frequently implicated are repetitive overhead activities (swimming, throwing, installing drywalls) or unaccustomed repetitive strenuous activity (gardening, golfing, shoveling snow). The impingement syndrome—impingement of the periarticular soft tissues between the greater tuberosity of the humerus and the coracoacromial arch—also plays a common role in overuse injuries.

The cause of impingement can be multifunctional. Glenohumeral instability can be atraumatic, as is commonly seen in swimming and throwing athletes, or can be post-traumatic, as often seen after a shoulder dislocation. Glenohumeral instability leads to increased translation of the humeral head in the anterosuperior direction, narrowing the subacromial space. The resulting impingement on the rotator cuff tendons causes inflammation and weakness. Also, imbalance between the rotator cuff muscles and the scapular stabilizing muscles (rhomboids, trapezius, levator scapulae) can result in excessive protraction and rotation of the scapula, resulting in inferior movement of the acromion and impingement.

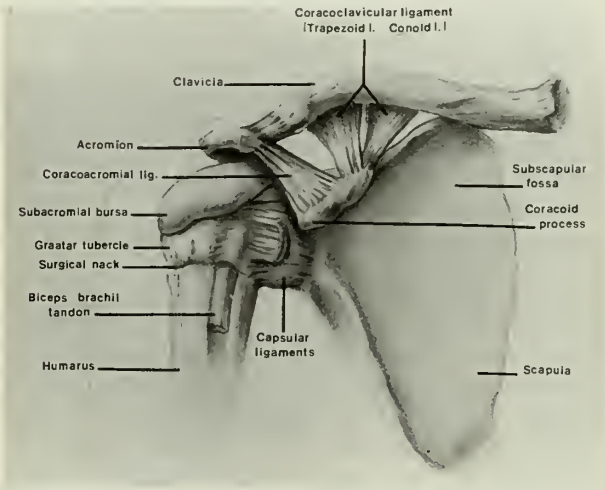
Often the inflammatory condition that causes a patient's pain is the result of impingement or instability (or both), combined with an acute overuse condition. Treatment of the acute inflammatory condition with attention to the underlying primary condition is important to full rehabilitation.

Trauma

Traumatic injuries of the shoulder can be classified as contusions, fractures, dislocations, subluxation, separation, or traumatic impingement.[3] Fractures typically involve the proximal humerus, clavicle, or both. Shoulder dislocations are usually anterior (90%) and, less commonly, posterior (10%). Unfortunately, there is an unacceptable incidence of missed diagnosis with posterior shoulder dislocations. Furthermore, shoulder subluxation is also an overlooked cause of symptoms in patients with pain or functional instability. Acromioclavicular separation is one of the most common injuries of the shoulder and of varying severity. Last, traumatic impingement often results in partial or complete rotator cuff tear, especially in persons older than 40 years.

Evaluating an Injured Shoulder

The proper evaluation of any shoulder injury begins with a thorough history and physical examination. With



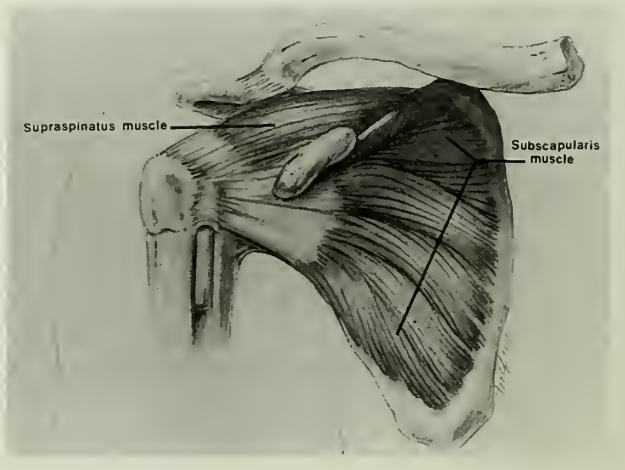


Figure 1.—Left and Right, Anterior views are shown of normal right shoulder anatomy. The major osseous and soft tissue structures are illustrated. The coordination of these structures results in a large functional range of motion.

injuries of the shoulder, the presenting symptom is most often pain with or without associated weakness. A patient with a previously undiagnosed shoulder injury may occasionally present with only a complaint of weakness. A careful history leads to a correct diagnosis in most cases. With both overuse and traumatic injuries, eliciting the precipitating event is most important. The mechanism of trauma, the direction of the force and shoulder position at the time of injury, and the patient's age, occupation, side of dominance, and history of previous shoulder disorders should be considered. With overuse injuries, pain with overhead or throwing activities may indicate impingement, instability, or both. Pain worse after rather than during use of the affected shoulder or pain at night implies an inflammatory condition. In patients in whom shoulder pain is not preceded by a history of overuse or trauma, a serious underlying cause, such as systemic arthritis, infection, neoplasm, or cardiac disease, needs to be excluded. Because of the coexistence of cervical disease, particularly in patients older than 55 years, all shoulder examinations should begin with a quick examination of neck motion.

Adequate exposure of both shoulders is mandatory so as not to miss any subtle asymmetry. Particular attention should be paid to the presence of obvious deformity due to fractures or dislocation, swelling, erythema, ecchymosis, or muscle wasting. Active range of motion (ROM) maneuvers are then performed and compared with those in the asymptomatic shoulder (Table 1). Because movements of the shoulder involve rotating the scapula, active ROM maneuvers should be viewed from behind as well. With overuse injuries, a painful arc of motion, usually between 60 and 120 degrees of abduction, is indicative of the impingement syndrome. A limitation of active ROM may be due to pain, weakness, or both. An inability to abduct the arm implies a complete rotator cuff tear. Partial rotator cuff tears are often accompanied by pain or demonstrable weakness on strength testing, with or without a limitation of active ROM. When active ROM is restricted, passive ROM may help to delineate the cause. With overuse injuries, passive ROM should not be restricted. Restriction of both active and passive ROMs suggests a frozen shoulder or adhesive capsulitis. In this instance, a limitation of external rotation is the most dramatic finding.

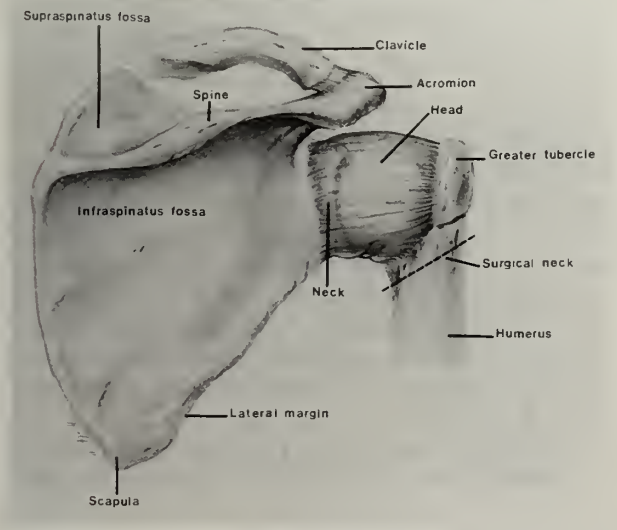
TABLE 1.—*Range of Normal Shoulder Motion*

Motion	*Range, degrees*
Flexion	180
Abduction	180
Adduction	75
Extension	50
External rotation*	65
Internal rotation*	80
External rotation†	90
Internal rotation†	70

*Arm at side.
†Arm abducted 90 degrees.

With traumatic causes, both active and passive ROMs may be restricted due to pain, especially when there is an associated fracture or dislocation. It is important, especially in suspected proximal humeral fractures or dislocations, to limit ROM testing so as to minimize the risk of injury to associated neurovascular structures. The diagnosis is dependent on a radiographic evaluation. Fractures or dislocations of the proximal humerus are difficult to diagnose, and it has been estimated that as many as 80% of posterior locked dislocations are missed by an initial treating physician.[1]

On completing passive ROM testing, strength testing of specific muscles (deltoid, rotator cuff) can be done to distinguish pain inhibition from lack of effort or actual weakness. Subtle weakness may be unmasked or magnified by repetitive contractions that use the effect of fatigue. Remember, weakness can result from muscle or nerve disease. Specific tests such as Jobe's and Speed's tests are useful for assessing supraspinatus and biceps



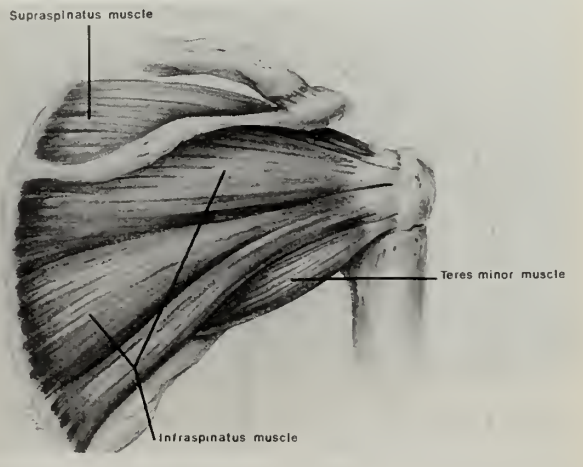


Figure 2.—Left and Right, Posterior views are shown of normal right shoulder anatomy.

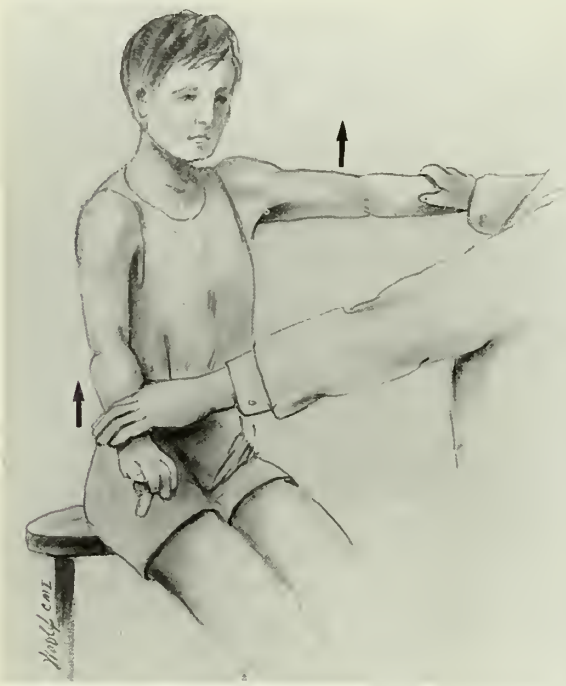


Figure 3.—Jobe's test for assessing supraspinatus integrity is illustrated: A positive test is pain and weakness on manual resistance with arms abducted to 90 degrees, brought forward into 30 degrees of flexion with the arm internally rotated.

tendon integrity, respectively (Figures 3 and 4). Hawkins' test for impingement is also useful (Figure 5).

Palpation is next done to locate the site of pain and disorder. With overuse injuries, pain is often generalized compared with the more localized pain of acute traumatic injury. The biceps tendon is readily palpable in its groove over the head of the humerus just medial to the greater tuberosity. Tenderness on palpation with pain on Speed's test is consistent with bicipital tendinitis. Tenderness to palpation over the acromioclavicular joint

Figure 4.—Speed's test for evaluating for bicipital tendinitis is shown: The test is "positive" (tendinitis is present) if pain is elicited with resisted flexion, adduction, and supination with the elbow extended.

Figure 5.—The diagram illustrates Hawkins' maneuver for assessing for impingement. Pain generated by forward flexion and internal rotation is a "positive" sign (impingement is present).

that worsens with adduction (cross-flexion with the arm at 90 degrees) suggests acromioclavicular arthralgia due to post-traumatic arthritis or to direct trauma with separation. Traumatic injury to the shoulder with associated fracture often has tenderness localized to the fracture site itself. With shoulder dislocation, often the humeral head can be palpated anteriorly or posteriorly relative to the glenoid, with obvious visual deformity on inspection.

Glenohumeral instability can be unmasked by several maneuvers. By palpating the humeral head through the deltoid and stabilizing the scapula with the other hand, attempts are made to glide the humeral head both anteriorly and posteriorly. An abnormal finding is when the head can be moved off the glenoid by more than 50%. The apprehension test can also be done to evaluate for anterior instability. With the patient sitting, the abducted arm is externally rotated while the examiner exerts anterior pressure on the proximal humerus. A "positive" finding is when the patient's muscles tense or the patient has a feeling of impending subluxation. Inferior laxity may be evident when direct longitudinal traction on the humerus results in a palpable defect beneath the acromion, the "sulcus" sign. Such an abnormal finding with vague glenohumeral pain and a history of the shoulder "popping out," with or without associated symptoms such as numbness, tingling, weakness, and episodes of a "dead arm," would support a diagnosis of shoulder subluxation.

Associated neurovascular structures should always be evaluated, especially in traumatic shoulder conditions, because injury to the axillary, musculocutaneous, and ulnar nerves as well as injury to the brachial or radial artery (or both) may be present.

TABLE 2.—*Radiographic Abnormalities of Shoulder Injuries*

Abnormality	*Description*
Traumatic	
Dislocation	Anterior Humeral head inferomedial to glenoid Hill-Sachs deformity
	Posterior Humeral head posterior to glenoid
Proximal humeral fracture	Nondisplaced Usually surgical neck
	Displaced >1 cm or >45 degrees of angulation
Acromioclavicular (AC) separation	1st degree No radiographic abnormality
	2nd degree <1 cm of displacement
	3rd degree >1 cm of displacement
Clavicle fracture	Middle third Most common
	Distal third Assess stability of AC joint
Impingement	A curved or hooked acromion—may be no radiographic findings
Chronic rotator cuff tear	Superior displacement of the humeral head
	Degenerative change in the undersurface of the acromion, humeral head, or both
Overuse	
Bursitis	Calcific deposits, subacromial space
Tendinitis	Calcific deposits, most commonly supraspinatus
AC joint degenerative arthritis	Osteoporosis, widening of AC joint, osteophytes
Osteolysis of the distal clavicle	Cyst formation, resorption, or both
Impingement	Ossification of AC ligament
	Subacromial spur(s)
	Curved or hooked acromion

Diagnostic Tests

Plain radiographs are the first imaging step in the diagnosis of shoulder injuries (Table 2).[4] Standard x-ray films should include anteroposterior (AP) and lateral projections in the scapular plane and an axillary view, motion and pain permitting. The lateral x-ray film in the scapular plane is also known as the Y view (transscapular). The axillary view allows for evaluation of the glenoid articular surface. Both are important in clearly diagnosing fractures and dislocations. A Hill-Sachs lesion—a compression fracture of the posterolateral aspect of the humeral head—will accompany 25% of first-time anterior dislocations and 75% of chronic dislocations.[1] Additional AP views in internal or external rotation will demonstrate the lesser and greater tuberosities of the humeral head, respectively, and are particularly useful in proximal humeral fractures. Specific views of the acromioclavicular joint (AP views with cephalad angulation) for suspected trauma should be done. These often include the opposite normal side for comparison with 10-lb weights (stress views). In cases of obvious acromioclavicular deformity, stress views are not necessary. To assess for clavicular trauma, an AP cephalad view is obtained. The most common site of a clavicular fracture is the middle third. Distal clavicle fractures are less common but more worrisome because of the possible disruption of the acromioclavicular joint.

To assess for overuse injuries, in addition to standard AP and axillary views, a true AP view (40 degrees postero-oblique projection) will show the glenoid in profile. The modified transscapular or outlet view will demonstrate the configuration on the acromion. Acromial structure is an important finding in patients with suspected impingement, as a curved or hooked acromion may contribute to this syndrome. Calcium deposits would suggest calcific tendinitis or bursitis, and this will frequently be missed unless a bright light is used to transilluminate the film. Degenerative changes about the glenoid, consisting of osteophytic lipping, sclerosis, or both, suggest instability or previous subluxation or dislocation. Radiographic evidence of the shoulder impingement syndrome should also be noted (see Table 2). Acromioclavicular joint disease may include degenerative arthritis. Osteolysis or cyst formation of the distal clavicle may be evident in someone with a history of acute injury or repeated stress on the shoulder. Although there is no consistent radiographic finding in acute or partial rotator cuff tears, indirect evidence of chronic rotator cuff tears can be seen radiographically, usually as a narrowing of the space between the acromion and the humeral head and sclerosis of the greater tuberosity.

Additional diagnostic studies such as computed tomography (CT), CT arthrography, magnetic resonance imaging (MRI), or fluoroscopy may be indicated in certain conditions.[4] Magnetic resonance imaging with contrast is becoming the diagnostic test of choice for illustrating soft tissue structures such as labral or rotator cuffs. Computed tomographic scanning is useful in trauma or for further delineating bony disease. Computed tomographic arthrography is useful when MRI scanning is not available. Fluoroscopy, once used to diagnose impingement, is being replaced by MRI where available.

Administering Diagnostic and Therapeutic Drugs

In patients with certain shoulder injuries, drugs may be administered for both diagnostic and therapeutic purposes. When pain precludes an adequate examination and motion is limited, particularly in overuse injuries, when the exact location of the shoulder pain is not clear, or when trying to differentiate apparent weakness from limited motion due to pain, the administration of a drug is a useful adjunct.[5] A selective use of a local anesthetic into the acromioclavicular, glenohumeral joint, subacromial bursa, or long head of the biceps may pinpoint the origin of the pain. A solution of 7 ml of 1% xylocaine is

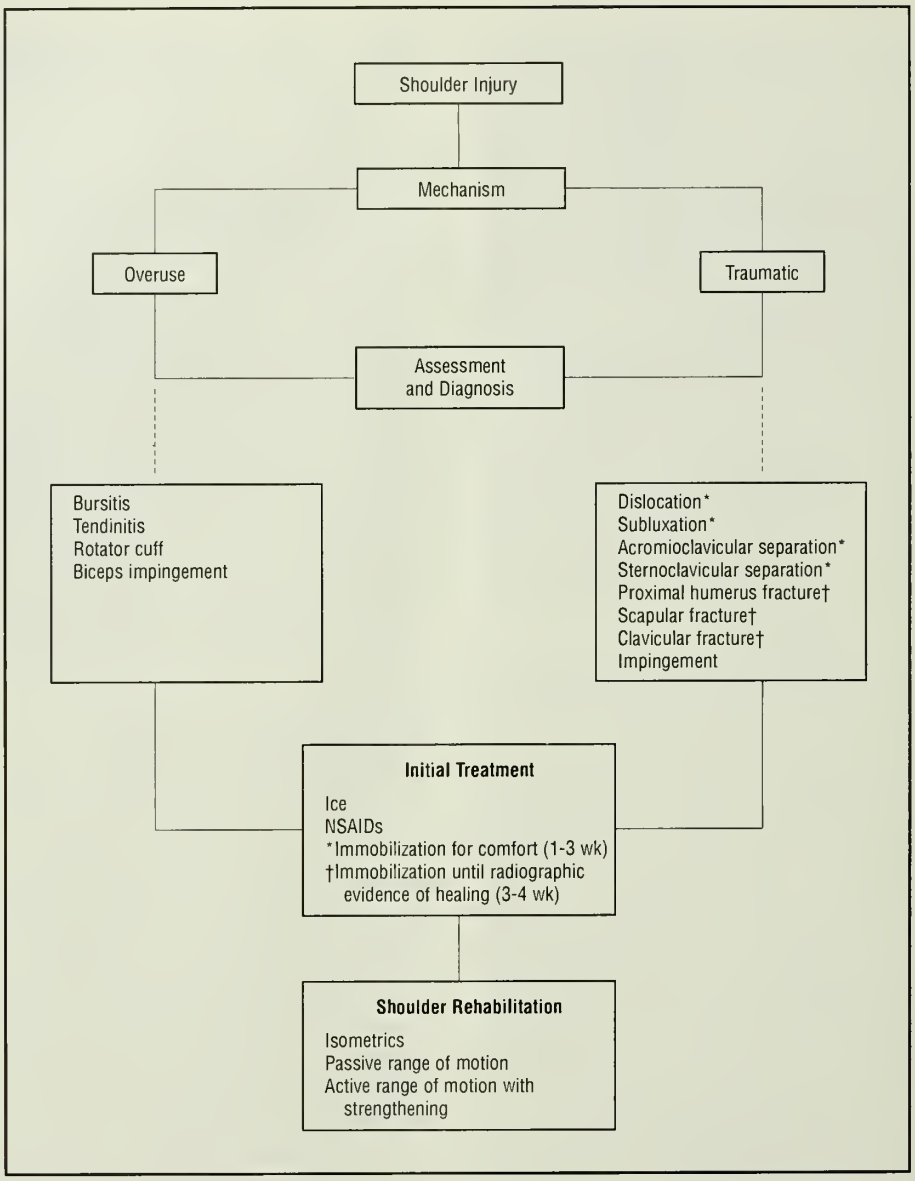


Figure 6.—The algorithm shows the general management of shoulder injuries. NSAIDs = non-steroidal anti-inflammatory drugs

administered under strict aseptic conditions. Specifically, administering the drug into the subacromial space will allow the physician to distinguish pain-inhibited motion due to an impingement syndrome, or bursitis, from weakness due to rotator cuff lesions (tendinitis, tears). Patients who have lessening of their pain or improvement in active motion after receiving a drug may benefit from the administration of a corticosteroid. This procedure should be done only by physicians experienced in such techniques.

Treating Injuries of the Shoulder

The following general treatment guidelines are for both overuse and traumatic shoulder injuries:

- Decrease the inflammatory response with ice, non-steroidal anti-inflammatory drugs (NSAIDs), or both;
- Alleviate pain;
- Properly immobilize the shoulder or use modified rest; and
- Properly rehabilitate to maximize the functional outcome (Figure 6).

In general, shoulder rehabilitation begins with isometric exercises, progressing to passive then active range of motion, incorporating strengthening of the rotator cuff and scapular stabilizing muscles (Figure 7). The specifics of treatment depend on the diagnosis.

Acromioclavicular Joint Injuries

Acromioclavicular joint injuries can be classified into first, second, and third degree, depending on the degree of separation.[6] A first-degree injury is noted by

swelling, pain, and ecchymosis, without obvious joint deformity, signifying minimal ligamentous disruption and instability. Treatment includes ice, pain medications, a sling for comfort, and early mobilization. A second-degree injury implies more tearing of the joint capsule with subluxation noted on stress x-ray films. Treatment is symptomatic but usually requires a longer period of immobilization (2 to 4 weeks) with a sling. If a patient is involved in contact sports or heavy labor, he or she should not resume full activities until full ROM and strength have been restored. In a third-degree injury, there is complete tearing of the acromioclavicular joint and the coracoclavicular ligaments. There is an obvious "step-off" on physical examination with an accompanying deformity on x-ray films. Third-degree injuries are further classified into grades 3 to 6, depending on the amount of coracoclavicular separation, associated damage to the surrounding deltotrapezius muscles, and the position of the displaced lateral end of the clavicle.[1] Grade 3 is characterized by an upward displacement of the clavicle and an increase in the coracoclavicular space by 25% to 100%. Grade 4 is characterized by an increased coracoclavicular space of 100% to 300%. Grade 5 involves associated posterior clavicular displacement with tearing of the deltoid and trapezius muscles. Grade 6 is a rare type in which there is not only complete disruption of the ligaments, but the distal clavicle is dislocated inferiorly.[1]

Conservative treatment with a sling for a grade 3 injury is appropriate, provided the patient understands that a permanent deformity may result.[7] Patients usually return to normal function. Surgical treatment is possible if symptomatic treatment fails. Treatment is controversial for athletes or those involved in heavy labor. For patients who want a cosmetically "normal joint," surgical therapy is recommended. Grades 4 to 6 injuries require orthopedic referral.

Clavicular fractures frequently involve the middle third (80%). These are generally treated with a figure-of-8 bandage or a sling.[3] Usually shortening or deformity results, but this is painless and does not affect function. The period of immobilization varies between four and six weeks. Referral is needed for open fractures or fractures associated with neurovascular injury. Distal third fractures are classified into types 1 to 3 according to the degree of coracoclavicular ligament and acromioclavicular joint injury. These should also be referred to an orthopedist.

Proximal Humerus Fractures

The majority (80%) of proximal humeral fractures can be treated by immobilizing with a sling and early range of motion based on fracture stability.[3] The period of immobilization varies from one to three weeks, depending on a patient's symptoms. Rehabilitation starts with pendulum exercises for passive ROM followed by isometrics and then active ROM. These fractures are further classified according to the presence or absence of displacement of the humeral head, the lesser and greater tuberosity, and the humeral shaft.[8] If any of these segments are displaced more than 1 cm, if there is more than 45 degrees of angulation, or if there is any question about the alignment or displacement, then consultation with an orthopedist is warranted.

Shoulder Dislocation and Subluxation

Shoulder dislocation often represents a higher-energy injury. Various methods of longitudinal traction with adequate anesthesia are used to reduce dislocations. These injuries are difficult to deal with in an office setting, and referral may be appropriate. Sling-and-swathe immobilization follows reduction to allow adequate capsular healing. Rehabilitation starts with isometric exercises, followed by passive and active ROM exercises within two weeks, avoiding the extremes of abduction and external rotation. The younger the patient, the greater the chances of redislocation. Associated rotator cuff tears in an older patient and labral injuries in a younger may result in persistent instability and may complicate the progress of a patient's rehabilitation. A failure to progress necessitates referral.

Traumatic shoulder subluxation is treated symptomatically, depending on the severity of the symptoms. Treatment can range from modified rest and restriction of motion to a sling with as long as two weeks of immobilization. We use a subluxation prevention program that emphasizes strengthening in a pain-free and restricted range while allowing the capsule to heal. Occasionally an associated labral injury will lead to functional shoulder instability.

Scapular Fractures

The treatment of most scapular fractures is immobilization by a sling for two to three weeks, followed by early ROM exercises. Scapular fractures that involve the glenoid, neck, acromion, or coracoid often require orthopedic consultation.[9]

Sternoclavicular Injuries

Injuries to the sternoclavicular joint are categorized into first-, second-, and third-degree injuries, depending on the degree of associated capsular disruption.[1] First- and second-degree injuries are treated symptomatically. Third-degree injuries with dislocation are fortunately rare. This is a serious injury if there is posterior displacement because of possible tracheal and large-vessel compromise. Immediate reduction is required in these cases.

Traumatic Impingement

A fall onto an outstretched hand or onto the proximal humerus can cause traumatic impingement. Initial treatment consists of ice, NSAIDs, and modified rest with or without a sling, depending on the severity of a patient's symptoms. As the patient's symptoms resolve, and if further strength testing of the shoulder shows a rotator cuff tear, an adequate period of rehabilitation (2 to 3

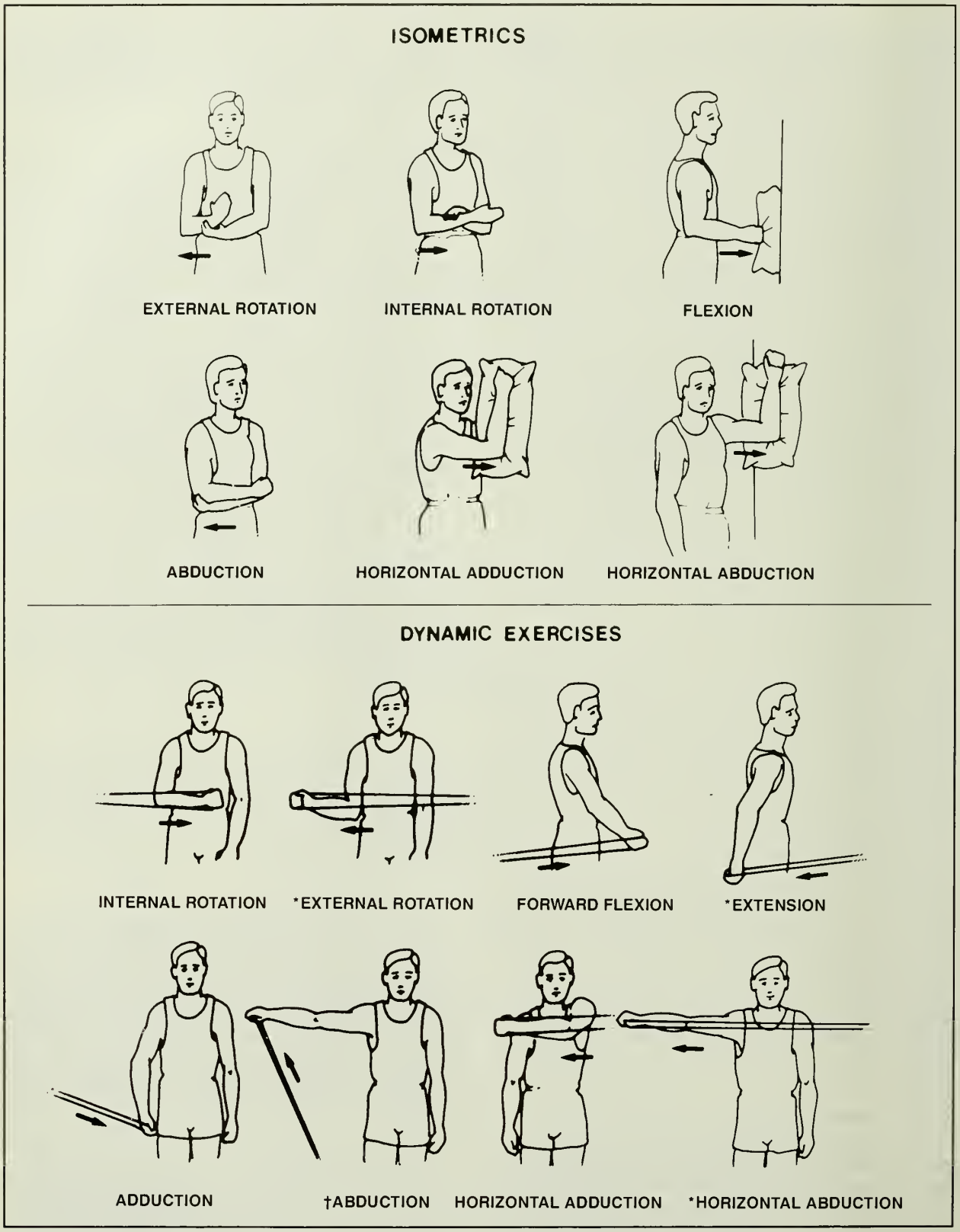


Figure 7.—Shoulder rehabilitation exercises are shown: Isometric **(top)** and dynamic **(bottom)** strengthening exercises are started once the acute inflammatory phase has resolved. All exercises should be done free of pain. For isometrics, hold a submaximal contraction for 5 seconds and repeat 10 times. Surgical tubing of various strengths is used for dynamic strengthening, generally incorporating 3 sets of 15 to 20 repetitions. * = subluxation prevention program: to neutral position (0 degrees) only, † = impingement protection program: to 45 degrees only

months) will often lead to good functional results.[10] Referral to an orthopedist is appropriate for possible surgical intervention if the patient fails to improve or the patient is an athlete or heavy laborer. Early recognition of this injury improves the subsequent outcome.

Overuse Injuries

Rotator cuff tendinitis, subacromial bursitis, bicipital tendinitis, and degenerative or post-traumatic arthritis should be treated initially with ice, NSAIDs, and modified rest until pain-free, followed by active ROM exercises and strengthening. If the impingement syndrome is present, the underlying biomechanical abnormality—glenohumeral instability, muscle imbalance, or poor throwing or swimming techniques—should be addressed. Also, specific rehabilitation should be directed toward rotator cuff strengthening and impingement protection, avoiding ranges that stress the shoulder. If these conditions fail to respond, administering a corticosteroid to the joint and physical therapy are often effective. Physical therapy modalities of ice, ultrasound, laser, and interferential therapy are useful adjuncts. In refractory cases, referral to an orthopedist is appropriate.

In summary, in treating common shoulder injuries, proper diagnosis and an aggressive rehabilitative approach are key to obtaining a good functional result and in preventing long-term disability.

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Conferences and Reviews

Current Management of Ductal Carcinoma In Situ

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Ductal carcinoma in situ represents a biologically and histologically heterogeneous group of lesions characterized by the proliferation of neoplastic epithelial cells confined to the ducts of the breast. Before screening mammography, ductal carcinoma in situ was considered uncommon; patients were usually diagnosed by a breast mass or bloody nipple discharge, and their treatment was mastectomy. Today it represents 20% to 30% of mammographically detected breast cancers and 10% to 15% of all diagnosed breast cancers in the United States. The invariable progression of this cancer to invasive breast cancer requiring mastectomy has been challenged, but because most patients have been treated with mastectomy, knowledge about ductal carcinoma in situ is limited and primarily based on retrospective data. Further insight will emerge from randomized prospective studies that are near completion. Currently available data indicate that breast-conserving treatments are valid alternatives to mastectomy for most patients with this disease.

(Barth A, Brenner RJ, Giuliano AE: Current management of ductal carcinoma in situ. West J Med 1995; 163:360-366)

Ductal carcinoma in situ of the breast is an early form of breast cancer in which malignant epithelial cells proliferate in the ductal system without microscopic evidence of invasion through the basement membrane into the surrounding stroma. Ductal carcinoma in situ seems to arise preferentially from the terminal ductal lobular unit.[1] The term "in situ carcinoma of the breast" was first used in 1932.[2] The median age of patients at diagnosis of this cancer is about 52 years, similar to that for invasive breast cancer.

The clinical presentation of this cancer changed dramatically with the increasing use of mammography in the early 1980s. Before this time, it represented only 0.8% to 3.2% of all breast cancers.[3,4] At the time of diagnosis, most of these patients had palpable breast masses, bloody nipple discharge, or Paget's disease of the nipple.[5] Today ductal carcinoma in situ is typically diagnosed in asymptomatic women undergoing screening mammography. According to the Surveillance, Epidemiology, and End Results (SEER) program, 13% of all breast cancers in the United States in 1990 were ductal carcinoma in situ[6]; for mammographically detected carcinomas, the rate was 20% to 30%.[7]

In this article we briefly review the natural history of this cancer and discuss unresolved issues of its diagnosis and treatment.

Mammographic Findings

The most frequent mammographic findings of ductal carcinoma in situ are microcalcifications, frequently clustered, with or without an associated soft tissue abnormality.[8,9] The submillimeter particles may be focal, ductal, or diffuse, and they have a variable size and shape; this pleomorphism is best recognized by magnification mammography. Most of the calcifications represent debris or secretions into the duct lumen, although calcifications can also be found in the duct epithelium.[10-12] These calcifications may be either curvilinear or amorphous and granular. Coalescence of intraluminal cellular debris may form a cast of the duct, characteristic of the comedo subtype (Figure 1). Comedo and noncomedo ductal carcinoma cannot be specifically identified by mammographic features, although calcifications of the comedo subtype generally (>75% of cases) are curvilinear and have casting.[13] Intraductal carcinoma may present with features that are atypical or not characteristic of a malignant process, such as an ill-defined density or calcifications not conforming to an identifiably malignant structure.[14]

Mammography may underestimate or overestimate the extent of disease. Areas of increased opacity associated with comedo ductal carcinoma frequently represent a stromal response to the tumor rather than invasive disease.[15] Conversely, the microcalcifications associated with noncomedo micropapillary and cribriform subtypes may be found in only a small fraction of the overall tumor.[16] Diffuse involvement may be present in asymptomatic patients.[17] Despite difficulties in diagnosing the type or extent of disease, the mammographic detection

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
NSABP = National Surgical Adjuvant Breast and Bowel Project

of suspicious microcalcifications in an asymptomatic patient, with its frequent correlation with noninvasive carcinoma, has become important in understanding and perhaps intercepting the natural history of the disease. Indeed, even the high sensitivity of magnetic resonance imaging has suffered from false-negative cases of ductal carcinoma in situ detected mammographically as suspicious clustered microcalcifications.[18]

Diagnosis

Today most cases of ductal carcinoma in situ are detected mammographically. This cancer rarely presents as a defined mass, although it may be found incidentally when excising a benign mass. Mammographic-localization breast biopsy is the standard approach to the management of a mammographic abnormality and is the usual method for definitively diagnosing intraductal carcinoma. Under mammographic guidance, a needle or guide wire is placed into the nonpalpable abnormality. The surgeon then makes an appropriate incision, preferably directly over the abnormality, and incises subcutaneous tissue until the mammographic abnormality is located with respect to the needle or wire. This area of the breast is then completely excised, and x-ray films of the excised specimen are taken to confirm that it contains the abnormality, which is then sent for histologic examination. It is often wise to do definitive surgical resection of highly suspicious lesions at the time of mammographic localization. If surgical margins are negative for disease, there is no need for a second operation; if they are positive, the breast area should be reexcised with a rim of normal tissue.[7,19]

Stereotactic core biopsy has recently gained popularity as a means of managing certain mammographic abnormalities.[20] In this technique, the mammogram is done using a dedicated instrument with computer capability; the computer calculates the location of the abnormality so that the operator can place a small cytology needle or a large-core (usually 14-gauge) cutting needle into the lesion. To achieve optimal results and minimize false-negative results, the histologic findings of stereotactic core biopsy must be carefully correlated with subsequent mammographic and physical findings.[21] If the biopsy reveals ductal carcinoma in situ, complete resection of the lesion and its surrounding tissue should be guided by standard mammographic localization techniques.

Histopathology

The histopathologic diagnosis of ductal carcinoma in situ of the breast is not always straightforward.[22] The spectrum of differential diagnoses ranges from benign

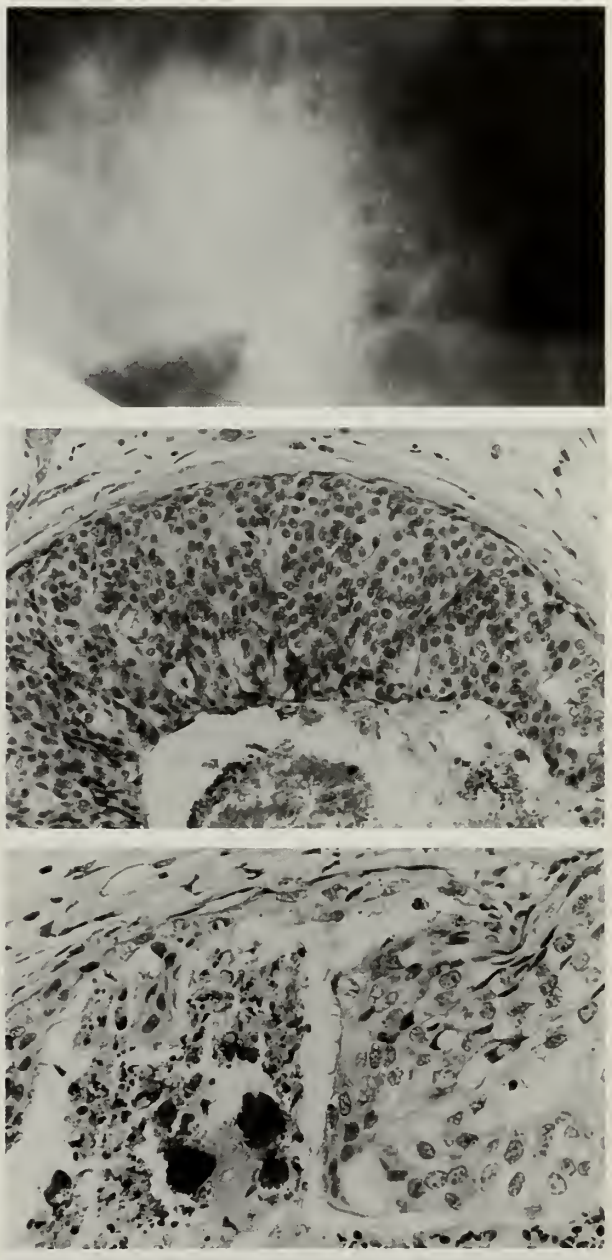

Figure 1.—In patients with comedo-type ductal carcinoma in situ (**top**), a mammogram shows a characteristic pattern of clustered pleomorphic microcalcifications with "casts." **Middle**, A corresponding photomicrograph (original magnification × 200) shows an involved duct with necrotic debris centrally. **Bottom**, Another photomicrograph (original magnification × 400) emphasizes the calcifications within the necrotic material.

atypical ductal hyperplasia to ductal carcinoma in situ with focal microinvasion. Although there is no universally accepted histopathologic classification of this cancer,[7,23,24] many pathologists divide it into noncomedo (papillary, micropapillary, cribriform, solid) and comedo, because the latter is characterized by an outer ring of malignant cells and an intraluminal necrosis (see Figure 1). Comedo ductal carcinoma is frequently associated with high nuclear grade, aneuploidy,[25] a higher prolifer-

ation rate,[26] *her-2/neu* overexpression,[27,28] and clinically more aggressive behavior.[29-31]

Natural History of Ductal Carcinoma In Situ

Because the vast majority of patients with ductal carcinoma in situ until recently were treated with mastectomy, the question of whether (and when) this cancer will transform into invasive breast cancer has thus far been addressed only by small retrospective studies. Patients in these studies were initially misdiagnosed with benign lesions and received no further treatment after excisional biopsy. Subsequent analysis of 96 patients from these studies[32] indicates that invasive breast cancer developed in 30 (31%) 0.5 to 24 years after excisional biopsy, generally during the first 10 years. With few exceptions, the invasive breast carcinoma was of the ductal type and located at the site of the original carcinoma in situ. These findings and the fact that autopsy series have revealed as much as a 14% incidence of intraductal carcinoma show that not all of these lesions progress to invasive breast cancer or become clinically significant.[33,34]

Nuclear grade,[30,31] ploidy,[25] proliferation rate,[26] and newer markers such as *her-2/neu* oncogene overexpression[27,28] or the absence of *Nm23* gene expression (suppressor gene of metastasis)[35] may allow a more accurate prediction of local recurrence or progression to invasive cancer.

Multicentricity and Multifocality of Ductal Carcinoma In Situ

Multicentricity is defined as ductal carcinoma in situ in a quadrant other than the index quadrant. A recent overview of ten published studies with a total of 553 mastectomy specimens revealed multicentricity in 161 cases (29%).[36] The reported incidence of multicentricity varied from 0% to 66%, however, probably due in part to differences in histopathologic techniques and definitions. Using a serial subgross and correlated radiographic-histologic method, a technique permitting three-dimensional reconstruction of the extent of ductal carcinoma in situ in millimeters, one study showed that 23% of the lesions involved more than one quadrant by continuous extension.[16] Only 1 of 82 mastectomy specimens (1.2%), however, had "true" multicentric distribution with separate lesions in opposite quadrants of the breast.

The biologic significance of occult ductal carcinoma in situ in a quadrant other than the index quadrant is unclear. As mentioned, the vast majority of patients receiving no further therapy after excisional biopsy have a recurrence in the same quadrant. The hypothesis that multifocality (same quadrant) is clinically more important than multicentricity (other quadrant) is supported by results of a study from the National Surgical Adjuvant Breast and Bowel Project (NSABP, project B06), in which the use of modified radical mastectomy was compared with that of segmentectomy plus radiotherapy for invasive breast cancer. This study inadvertently included 78 patients whose carcinoma in situ had been incorrectly diagnosed as invasive disease. All local recurrences after breast-conserving surgery and all residual carcinomatous foci in the mastectomy specimen were in the quadrant of the initial lesion,[37,38] supporting the findings of the previously described study.[16]

Incidence of Occult Invasion

The reported incidence of invasive disease at mastectomy in patients with a biopsy diagnosis of ductal carcinoma in situ (occult invasion) varies from 2% to 21%,[39] although the incidence of occult invasion following segmental resection with histologically normal margins is unknown.[37] In two investigations,[7,30] a serial subgross and correlated radiographic method revealed occult invasion in mastectomy specimens from 13 of 111 patients (11.7%) who had undergone excisional biopsy of their intraductal carcinoma. All occult invasive cancers were associated with a malignant lesion of greater than 45 mm, and the incidence of occult invasion approached 50% for lesions of greater than 55 mm. Another study found foci of occult invasion in 11% of patients with palpable ductal carcinoma in situ but in no patients with clinically occult disease.[40] These results suggest a correlation between the size of a malignant lesion and the incidence of occult invasion.

Axillary Lymph Node Metastasis

In an overview of nine studies with a total of 754 patients, the incidence of axillary lymph node metastasis for patients with ductal carcinoma in situ was 1.7%.[32] For mammographically detected, nonpalpable disease, the rate was 0%.[41] There is wide agreement, therefore, to omit formal axillary lymph node dissection in patients with this disease. Some authors, however, advocate removal of the axillary nodes in patients with palpable extensive ductal disease, who have a higher risk of occult invasion.[40,42]

Treatment

Mastectomy

Until recently, most patients with ductal carcinoma were treated by mastectomy. This approach has a high cure rate. In 15 published studies having a total of 1,411 patients (Table 1),[3,5,38,43-54] the mean local recurrence rate after mastectomy was 1.0% (95% confidence interval [CI], 0.5% to 1.5%), and subsequent mortality from metastatic breast cancer was 1.3% (95% CI, 0.7% to 1.9%). Because many of these patients had large palpable lesions, the few local and distant recurrences were most likely due to occult invasion.[30,41]

Breast-Conserving Surgical Therapy and Irradiation

In patients with invasive breast cancer, lumpectomy followed by breast irradiation yields recurrence rates

TABLE 1.—*Local Recurrence and Cause-Specific Death Rates Following Mastectomy for Ductal Carcinoma In Situ*

Source	Potients, No.	Follow-up, yr	Locol Recurrence, No. (%)	Died of Diseose, No. (%)
Farrow, 1970[43]	181	2-20	2	4
Ashikari et al, 1971[5]	110	1-10	2	1
Westbrook and Gallagher, 1975[44]	60	5-25	1	0
Brown et al, 1976[45]	39	1-15	0	0
Carter and Smith, 1977[46]	38	6.2	0	1
Rosner et al, 1980[3]	182	5	- -	3
Lagios et al, 1982[47]	53	3.7	2	1
Von Reuden and Wilson, 1984[48]	47	1-22	0	0
Sunshine et al, 1985[49]	68	>10	0	3
Fentiman et al, 1986[50]	76	4.8	1	1
Schuh et al, 1986[51]	51	5.5	0	1
Kinne et al, 1989[52]	101	11.5	1	1
Ciatto et al, 1990[53]	210	5.5	3	1
Fisher et al, 1991[38]	28	7.1	0	1
Silverstein et al, 1995[54]	167	6.5	2	0
Total	1,411		14 (1.0)	18 (1.3)

comparable with those of mastectomy,[55-57] provides better cosmesis than mastectomy, and may be followed by possibly curative salvage mastectomy if the cancer recurs locally. Breast-conserving therapy (excision and radiation therapy) has therefore been explored for ductal carcinoma. A review of seven published studies with a total of 968 patients (Table 2)[38,54,58-62] shows a mean local recurrence rate of 8.9% (95% CI, 7.1% to 10.7%). In the studies with longer follow-up, approximately 50% of the recurrences were invasive.

A nonrandomized multicenter study emphasizes the importance of adequate follow-up for ductal carcinoma in situ: the local recurrence rate was only 6% at 5 years but increased to 16% at 10 years[59] and 19% at 12 years.[63] A multivariate analysis showed that 20% of the comedo-type lesions with a high nuclear grade recurred at 8 years, compared with only 5% of other lesions (P = .017).[31] The increased local recurrence rate for high-grade comedo ductal carcinoma did not significantly affect survival, however. Despite a recurrence rate of 19%, half of which were invasive, the 12-year cause-specific survival rate in this study was 96%,[64] which was attributed to an early detection of recurrences and high salvage rates with mastectomy. The importance of nuclear grade in this malignant neoplasm was also demonstrated in a nonrandomized study in which 133 patients were treated with breast-conserving surgical therapy and irradiation.[54] With a median follow-up of 94 months, the 8-year local recurrence rate was 34% for high-grade disease, 10% for intermediate-grade, and 0% for low nuclear grade. The overall local recurrence rate in this series was 7% at 5 years and 19% at 10 years. Actuarial 10-year breast cancer-specific survival was 97%. In a subsequent study, the same investigators used the presence or absence of high nuclear grade and comedo-type necrosis to develop a novel prognostic classification that created three different subgroups of patients with intraductal carcinoma, each with a statistically different probability of local recurrence.[65] Although several studies suggest that radiation therapy tends to delay recurrence,[30,54,59,66] this possibility must be investigated by randomized trials using comparable patients and observation periods.

Since 1985, several multicenter studies have been initiated in the United States and Europe.[67] The results of only one randomized trial, however, NSABP B17, have been published so far.[61] In this study, 818 patients were randomly assigned to treatment with excision alone or

TABLE 2.—*Recurrence After Breast-Conserving Therapy (Excision and Irradiation)*

Source	Potients, No.	Follow-up, yr	Recurrences, No. (%)		
			Totol	Invosive	Noninvosive
Haffty et al, 1990[58]	60	3.6	4	1	3
Fisher et al, 1991[38]	27	7.1	2	1	1
Solin et al, 1991[59]	259	6.6	28	14	14
Silverstein et al, 1995[54]	133	7.8	16	8	8
Cataliotti et al, 1992[60]	34	7.8	3	3	0
Fisher et al, 1993[61]	399	3.6	28	8	20
Ray et al, 1994[62]	56	5.1	5	1	4
Total	968		86 (8.9)	36 (42)	50 (58)

TABLE 3.—*Recurrence After Wide Local Excision Only*

Source	Potients, No.	Follow-up, yr	Recurrences, No. (%)		
			Totol	Invasive	Noninvosive
Arnesson et al, 1989[72]	38	5	5	2	3
Carpenter et al, 1989[73]	28	3.2	5	1	4
Gallagher et al, 1989[74]	13	8.3	5	3	2
Lagios et al, 1990[7]	79	5.7	10	5	5
Fisher et al, 1991[38]	21	7.1	9	5	4
Silverstein et al, 1992[75]	26	1.5	2	1	1
Schwartz et al, 1992[29]	72	4	11	3	8
Cataliotti et al, 1992[60]	46	7.8	5	5	0
Fisher et al, 1993[61]	391	3.6	64	32	32
Total	714		116 (16)	57 (49)	59 (51)

excision followed by irradiation. The mean extent of malignant lesions was 13 mm, and 88% were less than 20 mm. All lesions were completely resected with normal margins. After a median follow-up time of 43 months, the actuarial 5-year local recurrence rate was 10.4% without irradiation versus 7.5% with irradiation ($P = .055$) for noninvasive cancers, and 10.5% without irradiation versus 2.9% with irradiation ($P < .001$) for invasive cancers. Of 83 recurrences, only 9 (11%) were not in the index quadrant. A recent reanalysis with a median follow-up of 57 months confirmed these 5-year results.[68] Recently published pathologic findings from the NSABP B17 study implicate comedo necrosis and margin status as independent predictors of local recurrence.[69]

The recommendation to treat all patients with ductal carcinoma with breast-conserving surgical treatment and irradiation[61,69] has been criticized by some.[70,71] These critics say that nonrandomized trials with long-term follow-up show that excision alone yields acceptable results in women with small and noncomedo ductal lesions. They further caution that recurrences in the irradiated group may simply be delayed, resulting in a doubling of the recurrence rate between five and eight to ten years, as observed in other studies.[54,64]

Wide Excision Only

Several nonrandomized studies have been done of the use of lumpectomy alone for ductal carcinoma in situ (Table 3).[7,29,38,60,61,72-75] Most of these studies, however, selected patients with better prognostic characteristics than those in studies of lumpectomy plus radiation therapy; this selection bias renders comparison difficult. An overview of nine studies with 714 patients (Table 3) reveals a mean recurrence rate of 16% (95% CI, 14% to 19%); about half the recurrences were invasive. Studies with a median follow-up of more than nine years reported recurrence rates as high as 40%.[38,74] The studies from the groups headed by Lagios[7,30] and Schwartz[29,76] deserve special attention because they selected patients according to strict criteria (solitary nonpalpable lesion, mammographically diagnosed ductal lesion of less than 25 mm, histologically normal margins). After a median follow-up time of 10.3 years, the 10-year local recurrence rate in the series from Lagios's group was 16% (written communication, September 1994). Although this was a highly selected patient population, the results match those of others for excision and breast irradiation.[59] Histopathologic correlation with outcome in the study from Lagios's group revealed a 10-year recurrence rate of 32% for high-grade ductal carcinoma versus 2.3% for low- to intermediate-grade lesions (written communication, September 1994), emphasizing again the prognostic importance of nuclear grade in this disease.

Conclusion

Ductal carcinoma in situ is a biologically and morphologically heterogeneous disease. Despite increasing knowledge about the disease, many important questions remain unanswered. Randomized trials under way in the United States and Europe may provide answers to unresolved issues such as the value and minimum extent of normal margins, marker indicators predicting invasion, recurrence, or both, and the role of breast irradiation and tamoxifen.[19,68,77,78] Important end points of these studies should include not only the local recurrence rate, which is significantly higher in patients treated with breast-conserving therapy, but also the long-term mortality from invasive breast cancer. Although there are no randomized data addressing these issues, published results currently indicate a 1% to 2% long-term risk of death from breast cancer following mastectomy and a 3% to 5% long-term risk following breast-conserving therapy. Although mastectomy remains the preferred method for the treatment of ductal carcinoma, available data indicate that breast-conserving treatments are a valid alternative for the majority of patients.

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* * *

The Abortion

She came across in the hands of paramedics
who had stuffed her full of packing
and wore her bright blood in their laps.
"Light bulb," their report read,
"self inflicted." She hissed
straight past the whispering
ER doors to us, the OR—
floor of last resort.

As we unravelled bandages
she went the color of old wax.
Stained shards tinkled to the floor
and clotted to our shoes
as we tried to keep her
(so sharded, so small,
the long ones imbedded in the blooming
bulb of uterus) and though we worked
to get her back, she bled out
on our clean white sheets.

Mitch, who gave the anesthesia,
pumping sweet air and oblivion,
helped me wrap the shroud
and then we dropped our blood-
drenched scrubs and all constraint
at the men's room door and together
in the little shower, we let the water,
hot as we could stand it,
wash over us.

ELLEN DUDLEY©
Marlboro, Vermont

Epitomes

Important Advances in Clinical Medicine

Allergy and Immunology

Daniel C. Adelman, MD, and Alan Goldsobel, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association, and the summaries were prepared under the direction of Drs Adelman and Goldsobel and the panel.

Steroid-Resistant Asthma

RECENT STUDIES demonstrate the importance of airway inflammation and immune activation in the pathogenesis of asthma. Glucocorticoids are the most potent anti-inflammatory therapy commonly used in this disease. Certain patients with asthma in whom occult sinusitis, gastroesophageal reflux disease, and environmental allergen exposure have been excluded still fail to have a satisfactory response even to combined inhaled and parenteral glucocorticoid therapy, and their asthma is considered "steroid-resistant." Many of these patients continue treatment with glucocorticoids despite having serious adverse effects and poor clinical response. It is important to differentiate these patients early because they may benefit from alternative approaches to treatment.

Patients with a morning baseline (before bronchodilator use) forced expiratory volume in one second (FEV_1) of less than 70% of the predicted value have steroid-resistant asthma if their morning prebronchodilator FEV_1 value fails to improve by 15% or more after a two-week course of oral prednisone (40 mg per day). In contrast, people whose asthma is steroid-sensitive and who have similar baseline FEV_1 values frequently will have an increased FEV_1 by 30% or greater after prednisone treatment. Patients with a history of steroid resistance should be carefully assessed for misdiagnosis, poor inhaler technique, noncompliance to medications, pharmacokinetic abnormalities in steroid absorption or elimination, persistent allergen exposure, or psychological disorders. Even after these confounding factors in asthma therapy are excluded, a small subset of patients remain whose asthma is poorly responsive to steroid use.

Studies of the peripheral blood and bronchoalveolar lavage (BAL) cells from patients with asthma reveal the presence of persistent eosinophilia and T-cell activation despite treatment with high-dose prednisone. Furthermore, BAL cells from the airways of patients with steroid-resistant asthma have a distinct pattern of cytokine gene expression and response to prednisone that differs from those found in patients with steroid-resistant asthma. Both before and after prednisone therapy, BAL cells from patients with steroid-resistant asthma have a substantially higher level of interleukin (IL)-2 and IL-4 gene expression than BAL cells from those with steroid-sensitive asthma.

Although there is a spectrum of glucocorticoid receptor-binding abnormalities in all patients with chronic asthma, patients with steroid-resistant asthma have the most extreme abnormality in their glucocorticoid receptors. Most patients with steroid-resistant asthma present with severe side effects from parenteral steroid therapy and a lack of benefit. Furthermore, their morning cortisol levels are generally suppressed by steroid therapy. T cells from most of these patients have a glucocorticoid receptor-binding defect that reverses in culture. This "type 1" defect is sustained in vitro by the presence of the combination of IL-2 and IL-4 and is thought to be an acquired defect. A second, less common group of patients with steroid-resistant asthma present with a history of no side effects from high-dose steroid therapy. These patients have normal glucocorticoid receptor-binding affinity but a markedly reduced number of glucocorticoid receptors per cell. The glucocorticoid receptor abnormality in "type 2" steroid-resistant asthma is irreversible and does not respond to coincubation with a combination of IL-2 and IL-4. These patients seem to have a primary steroid resistance syndrome.

Most patients with steroid-resistant asthma have the acquired form of this disorder. A number of factors can contribute to the development of steroid resistance. The overuse of certain drugs, particularly inhaled β-agonists, can reduce steroid responsiveness. Inflammation and immune activation are likely to play a key role in altering glucocorticoid receptor binding and, therefore, steroid responsiveness. In this regard, cytokines can induce transcription factors that directly interact with glucocorticoid receptors and interfere with their ability to bind to DNA.

The degree of change in glucocorticoid receptor binding affinity may be related to the magnitude of airway inflammation.

Although patients with steroid-resistant asthma may respond to extremely high-dose glucocorticoid therapy, recent studies have identified several promising treatment regimens as alternatives to parenteral glucocorticoid therapy. Rigorous clinical trials will be needed to evaluate these potential therapies, which include the newer generation of inhaled steroids (such as budesonide and fluticasone propionate), cyclosporine, and intravenous γ-globulin therapy. Characteristic of these treatments is the variable response observed among patients. An understanding of the mechanisms by which glucocorticoids and alternative drugs fail to resolve inflammation in asthma may provide important insights into the pathogenesis of chronic asthma and result in a rational design of innovative and more effective treatment approaches.

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Effectiveness of Allergy Immunotherapy for Asthma

ALLERGY IMMUNOTHERAPY is the technique of administering increasing doses of an extract of specific allergens that, on natural exposure, cause allergic patients to respond with allergic symptoms. The goal of this therapy is to alter patients' immunologic response to specific allergens and thereby ameliorate symptoms. Allergy immunotherapy has been practiced since 1911; in numerous double-blind, placebo-controlled studies, it has been shown to be effective management of allergic rhinitis and Hymenoptera (insect venom) sensitivity. The results of controlled studies of allergy immunotherapy in patients with asthma have been less clear, partly due to the subjectivity of symptoms used to measure improvement. Recent research has focused on objective assessments of improvement, the mechanism of action, and cost-effectiveness, which has added new weight to the evidence favoring immunotherapy for this disorder.

Clinical studies in animal-induced asthma have shown lessening of overall symptoms and a delay in the onset of symptoms. In addition, following immunotherapy with cat allergens in patients with cat-allergic asthma, specific sensitivity was substantially reduced. Nonspecific bronchial reactivity to histamine was also decreased. Similarly, studies involving house dust mites have also shown clinical improvement and a reduced bronchial response to challenge with dust mite extract. In addition, a significant reduction has been shown in the late response to bronchial challenge (4 to 8 hours after challenge, a cellular and inflammatory infiltrate is produced that is responsible for chronic asthma).

Clinical studies with pollen have also shown clear clinical improvement. A recent five-year, double-blind, placebo-controlled study of allergy immunotherapy in patients with asthma to ragweed, sponsored by the National Institute of Allergy and Infectious Diseases, demonstrated improvement in patients who were immunized against ragweed; they had reduced clinical symptoms, skin test sensitivity, immunoglobulin E measurements, and nonspecific bronchial sensitivity to methacholine and bronchial provocation tests when compared with placebo-treated control patients.

Several double-blind, placebo-controlled trials of immunotherapy for grass pollen allergy have shown that there is a pronounced reduction of the characteristic $CD4^+$ T-cell and activated eosinophil cellular infiltrates during the late-phase response. In addition, allergy immunotherapy appears to induce a "switch" from a "proallergic" T-cell phenotype (TH-2) to an "allergy-suppressing" T-cell phenotype (TH-1).

Allergy immunotherapy adds about $2.12 per day to the first-year cost of therapy, but only $0.47 per day in the subsequent years. These modest increases in cost are more than offset by savings from reduced medication costs and are associated with substantially reduced morbidity and mortality.

Allergy immunotherapy in selected patients with allergic asthma, using well-characterized standardized antigens, has been shown by objective measures to be effective clinically and cost-saving. In the final analysis, the selection of patients for immunotherapy must be dictated by the severity of the disease, the ineffectiveness of environmental controls, the necessity for frequent medications, and the potential, although small, for a systemic reaction to the immunotherapy itself.

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Changing Face of HIV/AIDS Care—Mother-Fetal and Maternal-Child HIV Transmission

HUMAN IMMUNODEFICIENCY VIRUS (HIV) disease is now the leading cause of death in adults aged 25 to 44 years in the United States. The World Health Organization contin-

ues to predict that 30 to 40 million persons will be infected with HIV by 2000. Globally, heterosexual transmission remains the predominant mode of spread. In the United States, epidemiologic studies reveal that HIV is increasingly prevalent in heterosexuals, racial and ethnic minority groups, women, poor people, and adolescents. More than 20,000 women in the United States have the acquired immunodeficiency syndrome (AIDS). Each year in the United States, 7,000 HIV-infected women give birth, and 25% of these infants become infected with HIV; AIDS is now the fifth leading cause of death in US children younger than 15 years. The recently completed AIDS clinical trial group study (ACTG076) evaluated the efficacy and safety of zidovudine in preventing maternal-fetal transmission in pregnant women with $CD4^+$ counts higher than 200×10^9 per liter (200 cells per mm^3). Administering zidovudine during pregnancy and delivery, as well as to infants during the first six weeks of life, reduced the risk of transmission by 66% ($P < .001$). The Food and Drug Administration has approved the use of zidovudine during pregnancy as a strategy to prevent vertical transmission. The US Public Health Service's official report summarized the study results, discussed limitations of the data, and issued recommendations for the use and monitoring of zidovudine during pregnancy. The long-term risks of fetal and neonatal zidovudine use are unknown.

Several factors, including high maternal viral load, prolonged rupture of membranes, and breast-feeding, increase the risk of vertical transmission. Recent reports on maternal viral load help to explain why, in general, only about 25% of pregnancies in HIV-infected women result in HIV-infected offspring. Determining the viral burden during pregnancy may identify women at highest risk and help direct counseling and treatment strategies. Quantitative polymerase chain reaction and other new methods of measuring the viral burden may be more powerful predictors of transmission than $CD4^+$ quantification or viral culture methods, but these are still being evaluated for clinical reliability.

Breast-feeding is also linked to vertical HIV transmission. Cases of AIDS have been reported in children whose mothers were infected by postpartum transfusions of HIV-infected blood. The transmission of the virus to the infant was thus thought to be related to breast-feeding during maternal primary infection when viral burden is extremely high. In developing countries, the benefit of breast-feeding, such as reduced infant mortality from diarrheal and other illnesses, is considered to offset the risk of HIV transmission. In the US, breast-feeding by HIV-seropositive women is strongly discouraged.

From the recent advances in maternal screening, viral quantification, and understanding of the predictors of transmission have emerged an encouraging picture of decreasing maternal-infant HIV transmission. Results from antiviral drug trials and epidemiologic reports, coupled with new technologies for quantifying viral load, provide us with a clearer image of the changing face of HIV infection and AIDS.

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Occupational Exposure to Latex

LATEX IS THE milky sap that is harvested from the rubber tree *Hevea brasiliensis*. During the manufacturing of latex products, many compounding agents are added. Adverse reactions to natural rubber products were first attributed to these added substances. Indeed, hand dermatitis to latex gloves, first reported 60 years ago, is usually a delayed (type IV) hypersensitivity reaction to thiuram or other additives. Evidence for immunoglobulin (Ig) E-mediated (type I) reactions to protein antigens in latex itself were first documented 15 years ago, and since then the incidence of such reactions has increased dramatically. This has been attributed to the implementation of universal precautions for infectious diseases that have greatly increased the use of latex gloves and apparently increased the antigenicity of latex products due to alterations in manufacturing to increase production. The amount of antigen in latex gloves is highly variable, ranging from 1 to 2,700 mg per gram. The most important factors in lowering the allergen content are leaching and steam sterilization. Laboratory studies have identified many possible antigens in latex, two in particular of 14.5 and 24 to 30 kd in size. The cornstarch used in latex gloves is itself nonallergenic, but latex particles can adsorb to the starch and become aerosolized, facilitating exposure.

The clinical presentation of latex allergy is variable and depends on the amount of available antigen in the product and the form of exposure. Reactions to gloves can be localized contact dermatitis or urticaria, but systemic urticaria and anaphylaxis have been reported. The most severe reactions to latex proteins have been associated with parenteral or mucosal contact, such as intraoperative exposure to gloves or gastrointestinal, oral, or genital mucosal exposures during barium enema or dental procedures.

Immunoglobulin E-mediated occupational reactions to latex products have been recognized since 1988. In one study of 57 health care workers and 67 other workers with occupational exposure to latex, the following symptoms were reported: contact urticaria in 79% of health care workers versus 72% of other workers, hand eczema in 42% versus 64%, conjunctivitis in 28% versus 16%, rhinitis in 16% versus 13%, facial edema in 14% versus 28%, generalized urticaria in 9% versus 13%, asthma in 2% versus 4%, and anaphylaxis in 7% versus 10%. Occupational allergy to latex antigen has been reported in surgeons, nurses, dentists, pharmacists, and radiology and other medical technicians. Recent surveys have found that 10% to 17% of all

hospital personnel, 7.4% of surgeons, and 5.2% to 10.7% of operating room staff are sensitive to latex.

The usual progression of symptoms seen in latex-allergic health care workers is first contact dermatitis or localized urticaria, and then systemic symptoms—generalized urticaria, rhinitis, asthma, and, rarely, anaphylaxis. Some nonmedical professions that involve latex exposure are kitchen work, the rubber industry, or the manufacture of rubber products such as toys, gloves, and rubber bands. The prevalence of latex allergy in these groups is less well known, but one recent study in a latex glove plant showed sensitization in 11% of workers.

The diagnosis of IgE-mediated latex allergy can be confirmed by skin prick or radioallergosorbent testing (RAST). There are currently no standardized commercial extracts for skin testing available in the United States, but such products are available in Canada and Europe. Several latex RAST allergens are available. Older RAST methods had only a 60% to 65% sensitivity rate, but newer tests recently approved by the US Food and Drug Administration have higher sensitivity rates.

Preventing occupational exposure of health care workers requires the use of nonlatex, low antigen-containing or powder-free gloves and latex substitutes for nonglove products. In operating rooms, the airborne latex allergen level can be high enough to cause respiratory symptoms in highly sensitized workers and patients. A future goal is the production of rubber products that have no or very low allergenicity.

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Value of Home Peak Flow Monitoring for Asthma Control

HOME PEAK FLOW MONITORING is recommended by the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program: Guidelines for the diagnosis and management of asthma for all patients with asthma who are aged 5 years and older. The guidelines suggest that measuring peak flow is necessary in the management of asthma, in much the same way that blood pressure monitoring is necessary to manage hypertension and blood glucose monitoring is necessary to manage diabetes mellitus. Yet, controversy and resistance surround the use of home peak flow monitoring for the management of asthma. Many physicians consider it burdensome, unreliable, and of questionable value. Others find that they lack the training to effectively use the daily measurement records their patients bring them.

The peak expiratory flow rate is the fastest flow rate that can be sustained for 10 milliseconds during a maximal expiratory effort after full inspiration. The value obtained, in liters per minute on a home peak flow meter, is effort-dependent and, when a maximal effort is made, indicates the caliber of large airways. Peak flow is abnormally decreased only in patients with moderate to severe airway obstruction. Except when extremely low, absolute values are an unreliable guide to the severity of airflow obstruction because the range of peak flow is not linear in its clinical importance. A change of 100 liters per minute is more relevant at the lower end of the scale than at the upper end; but trends within individual patients are valuable over time.

Home peak flow monitoring is not without pitfalls, as the measure is effort-dependent, requiring a maximal expiratory effort. To increase the reliability of measurements, patients are instructed to make three maximal attempts and record the highest value. Performance technique may wane with time, however, and the best approach is to have the patient demonstrate the peak flow expiratory maneuver at each office visit. Other problems include inaccurate reading or recording and fungal growth inside the meter. The greatest pitfall of the current meters is their reliance on consistent and accurate patient self-measurement. Compliance can become a problem if the patient sees no value in making the daily measurements. Similarly, if patients are asked to make measurements and fill out diaries without being told what the numbers mean and what to do in response, compliance decreases considerably with time. Only when peak flow monitoring is tied to action plans that require the patient to understand the value and self-manage the illness do results improve.

When patients use peak flow measurements, both compliance and clinical outcomes appear to improve. Health care professionals must understand and explain clearly the implications of peak flow values for individual patients. When records indicate that a peak flow value has fallen substantially, the opportunity should be taken to explore the history of that event and to teach the patient the correct and most appropriate actions to take. When patients have taken appropriate action, it is important to use the opportunity to provide positive reinforcement. The directions for actions to take to manage asthma exacerbations must be explicit and specific to a person's clinical profile. For example, when a peak flow value falls to a predetermined level, the patient should be instructed to use rescue medication.

There are several possible advantages of home peak flow monitoring. Episodes of airflow obstruction, for which treatment is indicated, can be identified. Patterns of peak flow that suggest increased risk, such as morning dips or wide diurnal variation, can be documented. By matching objective measurements to subjective sensations, symptom recognition may be enhanced, especially in those with a poor perception of airflow obstruction. Home monitoring allows peak flow-guided self-management using self-adjusted medications—a true partnership approach between professional and patient. Finally, peak flow monitoring may result in more appropriate, less frequent, use of inhaled β-agonist rescue medication.

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Caution With Inhaled Corticosteroids in Childhood Asthma

THE USE OF INHALED corticosteroids for the treatment of childhood asthma is increasing for almost all degrees of severity. The corticosteroid aerosols available in the United States for asthma (beclomethasone dipropionate, triamcinolone acetonide, and flunisolide) are all highly effective. Nevertheless, many physicians are reluctant to use them, especially in children, because of uncertainty and controversy regarding the associated risk.

Only 10% to 15% of inhaled corticosteroids administered by a metered-dose inhaler is deposited in the lungs. Most of each dose is deposited in the posterior pharynx and mouth and is ingested and variably absorbed through the gastrointestinal tract. Inhaled corticosteroids are also absorbed directly through the lungs. Nasal delivery of topical corticosteroids for rhinitis may also contribute to systemic absorption.

Although there has always been a concern of increased susceptibility to infection with the use of inhaled corticosteroids, 20 years of experience, particularly with beclomethasone dipropionate, has shown that the incidence or severity of viral or bacterial infections in immunocompetent patients is not increased. Caution should be used, however, in children who are immunocompromised or who have tuberculosis or other chronic infection of the lungs.

Oropharyngeal or laryngeal candidiasis or dysphonia due to local effects on laryngeal muscles can complicate inhaled corticosteroid therapy. It is uncommon to need to discontinue treatment of these complications, however. Mouth rinsing after dosing and the use of a spacer device are effective remedies for these local problems.

The use of oral corticosteroids is well established as a cause of growth retardation in children, so their use in this population has been closely monitored. Data from several long-term clinical trials have shown no effect on growth in asthmatic children at doses of less than 800 mg per day. Exceptions to this include recent reports of a reduction in lower leg growth over a short-term period of treatment with 800 mg per day of budesonide and a decrease in growth velocity in prepubescent boys using 400 μg per day of beclomethasone diproprionate. Examining the effect of inhaled corticosteroids on growth in children, however, is complicated by studies showing that severe asthma without inhaled corticosteroid therapy can be associated with delayed puberty and growth rates and that growth velocity may not correlate with final adult height.

Alterations in bone metabolism leading to osteoporosis after long-term inhaled corticosteroid use is also a possible concern. Inhaled corticosteroids clearly have an effect on bone metabolism when sensitive markers of biochemical bone turnover and deposition (such as urinary hydroxyproline, osteocalcin, or alkaline phosphatase) are measured. Reduced bone mineral density has been noted in adults, but not children, on long-term inhaled corticosteroid therapy, although results have often been complicated by the concomitant administration of oral corticosteroids. To date, there is no information to suggest that treatment solely with inhaled corticosteroids leads to clinically important osteoporosis or fractures.

Inhaled corticosteroid therapy can lead to alterations in hypothalamic-pituitary-adrenal axis function at almost any dose when sensitive markers are examined. But only rare anecdotal reports of problems of clinical insufficiency or Cushing's syndrome have been published. The morning serum cortisol value is rarely affected by inhaled corticosteroid use unless the dose is high. The clinical meaning of alterations in more sensitive HPA axis markers is unknown. Thus, steroid replacement therapy for children on inhaled corticosteroid therapy who are undergoing a surgical procedure is not generally necessary.

The different inhaled corticosteroid preparations do have varying degrees of systemic absorption, but whether these differences in systemic bioavailability have any clinical relevance with regard to toxicity at conventional doses is still not known. The trend toward the use of higher doses of inhaled corticosteroids may make these differences more important because the systemic effects are dose related. Children can vary widely in their susceptibility, probably because of intrinsic differences in pharmacokinetics and end-organ sensitivity. Inhalation technique, the use of a spacer, mouth rinsing, and dosing frequency are other determinants that likely contribute to the systemic effects of inhaled corticosteroids.

We can expect recommendations in the future for more aggressive use of inhaled corticosteroids for children with allergic disease. The systemic problems of inhaled corticosteroids in most patients on low to moderate conventional doses are inconsequential. Higher doses are more effective but also more active systemically. When compared with the use of oral steroids, the tradeoff is likely still in favor of high-dose inhaled corticosteroids. The actual adverse systemic effects from the long-term use of intermediate- or high-dose inhaled corticosteroids in children is still unknown, and this must be kept in mind when prescribing prolonged inhaled corticosteroid therapy in this population.

Until more information is available, the following recommendations or precautions should be followed with inhaled corticosteroid treatment in children:

- Use the lowest effective dose of inhaled corticosteroids, preferably below 800 μg per day (some asthma experts recommend beginning treatment with a nonsteroidal anti-inflammatory medication such as cromolyn sodium or nedocromil);

- Use other nonmedical approaches, such as environmental control measures and immunotherapy, if indicated, in an attempt to keep the total inhaled corticosteroid dose as low as necessary;
- Use a spacer device with all inhaled corticosteroid preparations to help reduce oral deposition and systemic absorption;
- Rinse mouth well after every dose; and
- Monitor growth carefully (height and weight) over time.

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Long-Acting β_2-Agonists and Their Role in Asthma Management

TWO LONG-ACTING β_2-agonists have been well studied, salmeterol (a derivative of albuterol), which became available in the United States in 1994, and formoterol, which is still under investigation. Both have prolonged bronchodilating activity of at least 12 hours, but formoterol has a 5-minute onset of action compared with 15 minutes for salmeterol. Affinity for the β_2-receptor is greater with salmeterol than with albuterol but less than with formoterol; salmeterol is uniquely β_2-specific. Inhaled salmeterol has been shown to be effective for at least 12 hours in preventing bronchoconstriction induced by methacholine, histamine, exercise, allergen, and hyperventilation of cold air.

Reports conflict about whether salmeterol provides anti-inflammatory protection in addition to bronchodilatation. Recent studies suggest that although, like other bronchodilators, salmeterol can block the early phase response to allergen challenge, it only partially inhibits the late allergic response that best correlates with bronchial hyperreactivity and chronic inflammation. Bronchoalveolar lavage fluid after several weeks of salmeterol treatment does not show a reduction in inflammatory markers.

Compared with the use of albuterol (180 μg 4 times a day), the use of salmeterol (42 μg twice a day) has repeatedly been shown to result in superior control of day and night asthma symptoms, higher peak flow measurements and forced expiratory volume in one second, and less need for the use of a rescue β_2-agonist. It has been particularly impressive in preventing nocturnal and exercise-induced asthma for as long as 8 to 12 hours. The use of salmeterol has resulted in improved asthma control even in patients receiving modest doses of inhaled corticosteroids (400 μg per day of beclomethasone).

Concern has recently arisen regarding a purported deterioration of asthma control in patients using inhaled β_2-agonists daily. A study of patients with asthma on daily inhaled salmeterol therapy for 12 months showed no deterioration of asthma control and no change in responsiveness to inhaled albuterol. But several studies have suggested that a prolonged administration (eight weeks) of salmeterol leads to tolerance to its protective effects against bronchoconstrictive stimuli such as methacholine and exercise. Finally, several cases of sudden respiratory arrest have been reported in patients on maintenance salmeterol therapy. No cause-and-effect relationship has been demonstrated, however. Revisions in the labeling of salmeterol suggest that salmeterol should not be used to treat acute asthma but only as a maintenance medication twice a day; salmeterol therapy should not be initiated in patients with substantial worsening or acutely deteriorating asthma; and salmeterol is not a substitute for inhaled or oral corticosteroids.

In conclusion, salmeterol is a potent, long-acting, β_2-agonist that may be helpful in patients with moderate or severe asthma who require several-times-a-day doses of a β_2-agonist despite maintenance anti-inflammatory therapy and in patients with nocturnal symptoms. Further studies are needed to clarify the precise indications for salmeterol use in asthma therapy and to further define its safety profile.

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Asthma and Air Pollution

ALTHOUGH THE INCREASE IN asthma morbidity and mortality has several causes, urban air pollution may have a prominent role. Air pollutants for which there is evidence of possible adverse respiratory health effects at ambient levels include ozone, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter of less than 10 μm in diameter (PM_{10}). Unlike workplace exposure standards that are designed to protect the average healthy worker, the federal ambient air quality standards are designed to protect even the most susceptible members of the general population. Because asthma is characterized by both nonspecific airway hyperresponsiveness and airway inflammation, persons with asthma are generally considered to have increased susceptibility to the respiratory health effects of inhaled pollutants.

Ozone is an oxidant pollutant that is generated from motor vehicle and other emissions by photochemistry in the atmosphere. A large percentage of the United States population lives in areas where the ozone levels are above the federal standard. Because ozone inhalation by normal subjects causes increased airway responsiveness and airway inflammation, it is somewhat surprising that most

controlled human exposure studies have not shown patients with asthma to have greater ozone-induced decrements in lung function than normal persons. Presumably this is because ozone-induced decrements are caused by neuromuscular mechanisms that limit deep inspiration rather than by bronchoconstriction. Epidemiologic studies in Los Angeles, California; Houston, Texas; and Atlanta, Georgia, however, have shown increased rates of asthma attacks when ozone levels are high. A possible mechanism by which ozone exposure might lead to asthma attacks is enhanced sensitivity to inhaled allergen as a consequence of increased airway inflammation. An enhanced immediate bronchoconstrictor response to inhaled allergen after ozone exposure was demonstrated in a study involving a small number of persons with asthma.

The principal source of NO_2 in outdoor air is motor vehicle emissions, but indoor levels often exceed those seen outdoors. The principal indoor source of NO_2 is gas cooking stoves. Like ozone, NO_2 is an oxidant pollutant, although it is less chemically reactive and thus probably less potent. The lack of a short-term averaging time in the current NO_2 air quality standard means that persons with asthma are not thought to be at risk of acute exacerbations after brief exposures. Controlled exposure studies of persons with asthma have produced inconsistent results, with some evidence of a subgroup with increased sensitivity. Limited data from epidemiologic studies of the effect of indoor NO_2 exposure on the risk of respiratory illness in children are also inconsistent.

Sulfur dioxide is an irritant gas that is primarily generated from the burning of sulfur-containing fossil fuel. Sulfur dioxide pollution is much more of a problem in the eastern United States than in the western states. In contrast to ozone, SO_2 has been clearly shown to induce acute bronchoconstriction in asthmatic patients at concentrations well below those required to induce this response in normal subjects. The current air quality standard for SO_2 is not adequately protective of persons with asthma, as there is no question that brief (<1 hour) exposures to low concentrations of SO_2 can induce bronchoconstriction in such persons. A recent study showed that an atmosphere containing both SO_2 and NO_2 increased the immediate bronchoconstrictor response to inhaled allergen in patients with asthma.

Particulate matter is a mixture of substances, often including both solid and liquid particles, particles of biologic origin such as fungal spores and pollens, and particles of varying size and acidity. The 10-μm-in-diameter cutoff of the current federal standard was selected to include only particles of respirable size. The primary sources of fine particulate pollution are power and heavy industrial plants, wood-burning stoves, and diesel-fueled motor vehicles. Although substantial progress has been made in reducing particulate pollution, there are still many communities in which the federal PM_{10} standard is exceeded. Epidemiologic evidence is accumulating that the current standard offers an inadequate margin of safety to protect persons with asthma. Several studies have found a strong correlation between PM_{10} levels and hospital admissions for acute respiratory illnesses (including asthma). A diary study of schoolchildren has documented an association between the PM_{10} concentration and lower respiratory tract symptoms, despite the fact that all PM_{10} measurements were below the current federal standard. Panel studies have also shown decreased peak expiratory flow values and increased use of asthma medications on days with elevated PM_{10} levels.

In summary, there is considerable evidence that persons with asthma are at increased risk of having exacerbations with exposure to ozone, $S0_2$, and PM_{10} pollution (there is less evidence for NO_2). Persons with asthma should be advised to refrain from exercising outdoors on smoggy days, especially during the afternoons when ozone levels are highest. They also should be advised to reduce exposure to emissions from combustion sources, including agricultural burning and wood-burning stoves or fireplaces. A major reason to continue a strong national effort to maintain outdoor air quality is to protect asthmatic children and adults.

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Genetic Basis of the Primary Immunodeficiency Syndromes

RECENT ADVANCES in molecular genetics have led to the mapping and identification of several of the primary immunodeficiency disorders. In the past two years, the specific gene defects of X-linked agammaglobulinemia, a new and rare form of severe combined immunodeficiency (SCID), and the X-linked hyperimmunoglobulin M syndrome were reported.

X-linked agammaglobulinemia was first described in 1952. Mapping studies showed that the defective gene in this disorder was located in the q22 region of the X chromosome associated with coding for the cytoplasmic Bruton's tyrosine kinase (Btk). Protein-tyrosine kinases (PTKs) are critical intermediaries in cellular proliferation and differentiation signals. They act by phosphorylating proteins that regulate the interaction of other constituents in the signal transduction pathway. Recent reported mutations in this gene include a complete deficiency of Btk expression and point mutations that interfere with Btk activity. The identification of these and other mutations in the Btk gene is leading to a greater appreciation of the function of this PTK in B lymphocytes.

Protein-tyrosine kinases also play an important role in signaling of the T-cell receptor. The four PTKs identified in T-cell receptor signaling include Lck, Fyn, Syk, and ZAP70. Investigators recently identified a 1-year-old girl

with an autosomal recessive form of SCID who had an unusual complete absence of $CD8^+$ T cells. Functional studies revealed an absence of normal triggering of cytoplasmic PTK activity, suggesting a critical defect in T-cell activation. Assays of the individual PTKs known to be involved in T-cell receptor signal transduction revealed a complete absence of the ZAP70 protein. Cloning of the messenger RNA from this patient's cells revealed a 13-base-pair deletion. Two other mutations have been identified in an unrelated family with children showing a ZAP70 protein deficiency and similar clinical symptoms. The ZAP70 gene has been mapped to chromosome 2, which is consistent with the autosomal recessive inheritance pattern of the defect.

The third primary immunodeficiency for which the gene defect has been recently identified is the X-linked hyperimmunoglobulin M syndrome. Patients with this syndrome fail to produce normal amounts of immunoglobulin (Ig) E, IgA, or IgG, and despite elevated quantities of IgM, their immune system is seriously compromised. Investigators in the early 1990s discovered the CD40 receptor molecule on B cells and its ligand and recognized the importance of this receptor-ligand pair for T- and B-cell communication. Once the CD40 ligand gene had been mapped to the X chromosome, several groups of investigators simultaneously reported defects in the CD40 ligand gene as the cause of the hyperimmunoglobulin M syndrome. Different types of mutations have been identified that result in disruption of the normal coding sequence of the gene, and all lead to failed immunoglobulin class switching.

Other defined molecular genetic errors in primary immunodeficiency disorders include point mutations and deletions of the adenosine deaminase (ADA) gene in SCID-ADA, point mutations in the purine nucleoside phosphorylase (PNP) gene in SCID-PNP, and mutations resulting in truncation of the γ chain of the interleukin-2 receptor in X-linked SCID.

Understanding of the cellular and molecular mechanisms underlying antigen-specific immune responses has led to the discovery of the genetic defects causing many of the primary immunodeficiencies. The rapidity of these discoveries is unprecedented in medical history. These discoveries will lead to strategies designed to directly treat these disorders with gene therapy.

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Alerts, Notices, and Case Reports

Necrotizing Fasciitis and Septic Shock Caused by *Vibrio cholerae* Acquired in San Diego, California

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NECROTIZING FASCIITIS is a disease that threatens life and limb by rapid invasion and destruction of the fascial planes by bacteria. Various pathogenic mechanisms enable the infectious process to spread uncontrollably, causing necrosis of the tissues, systemic and vascular collapse, and often death. This is a medical and surgical emergency requiring a team approach for effective treatment. Immediate, aggressive surgical intervention with wide debridement to healthy tissue is required, and subsequent "second-look" operations in one or two days is indicated. In some cases a third, fourth, and more operations are necessary.

Necrotizing fasciitis can be caused by a variety of bacteria, both gram-positive and gram-negative, aerobic and anaerobic, cocci and bacilli. Specific organisms include groups A, B, C, and F streptococci, peptostreptococci, clostridia, *Vibrio vulnificus*[1] and other noncholera *Vibrio* species, *Aeromonas hydrophila*,[2] and other synergistic combinations of aerobic and anaerobic bacteria.

Infection with *Vibrio vulnificus* and other noncholera *Vibrio* species is a well-described cause of necrotizing fasciitis[3] that has a higher incidence in patients with cirrhosis, hemochromatosis, and hematologic malignancy.[4] Most reports of this disease have been related to exposure of traumatized tissue or to the ingestion of oysters and other shellfish from the Gulf of Mexico.[5,6] In contrast, although *Vibrio cholerae* strains are frequently isolated in this region, we could not find any documentation of necrotizing fasciitis associated with this organism.

We report a case of fulminant necrotizing fasciitis and sepsis syndrome due to a *V cholerae* non-O1 acquired in the city of San Diego, California, where this organism is rarely encountered.

(Wagner PD, Evans SD, Dunlap J, Ballon-Landa G: Necrotizing fasciitis and septic shock caused by *Vibrio cholerae* acquired in San Diego, California. West J Med 1995; 163:375-377)

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Report of a Case

The patient, a 51-year-old man, presented to the emergency department after the sudden onset of exquisite right lower extremity pain, swelling, and advancing erythema that had awakened him from sleep approximately 12 hours earlier. The patient had insulin-dependent diabetes mellitus of adult onset, and because of a chronic plantar ulcer of the right foot and several past episodes of cellulitis and osteomyelitis, he had had a right transmetatarsal amputation and amputation of the fourth and fifth digits of his left hand. He had attended a "wild" social event at a men's bathhouse the night before his presentation that included the use of alcohol and amyl nitrite. He thought he was having another bout of cellulitis, although he reported much more severe lower extremity pain with this episode.

On physical examination in the emergency department, the patient was moderately obese, appeared acutely ill and anxious, and had a temperature of 39.2°C (102.6°F), heart rate of 130 beats per minute, respiratory rate of 30 breaths per minute, blood pressure of 140/90 mm of mercury, and normal oxygen saturation while breathing room air as measured by pulse oximetry. His lungs were clear, he was tachycardic, and his abdomen was normal without hepatomegaly. The right lower extremity showed his past transmetatarsal amputation, and the skin on his ankle and leg was warm, erythematous, swollen, and tense to the knee, but without crepitus or edema. There was extreme tenderness to the midthigh. There were no blisters or foul-smelling discharge, and pulses were not palpable below either inguinal region. On the right foot there was a purulent 2-cm plantar ulcer extending into the muscle. The left lower extremity was notable only for multiple scars on the lower leg from previous operations. His left hand had previous skin grafts, and the fourth and fifth fingers had been amputated.

The leukocyte count was 2.8×10^9 per liter (2,800 per mm^3) with a differential cell count of 0.71 (71%) polymorphonuclear leukocytes, 0.15 (15%) lymphocytes, 0.12 (12%) band forms, and 0.01 (1%) monocytes. The hemoglobin level was 147 grams per liter (14.7 grams per dl), the hematocrit was 0.435 (43.5%), and the platelet count was 154×10^9 per liter (154,000 per mm^3). The results of all other laboratory tests were initially normal. The patient was admitted for treatment of a presumed right lower extremity cellulitis, and a regimen of the combination of ticarcillin disodium and potassium clavulanate was started.

On the second hospital day, the patient remained tachycardic and tachypneic, and fever, chills, and hypotension developed. A repeat leukocyte count was 6.6×10^9 per liter with a differential count of 0.33 polymorphonuclear leukocytes, 0.12 lymphocytes, and 0.55 band forms. The color of the right lower extremity had changed to a deep red with a faint blue hue to the midcalf, and several discrete, black, necrotic bullae had erupted along the anterior and medial aspect of his leg (Figure 1). There was no crepitus. A diagnosis of necrotizing fasciitis was

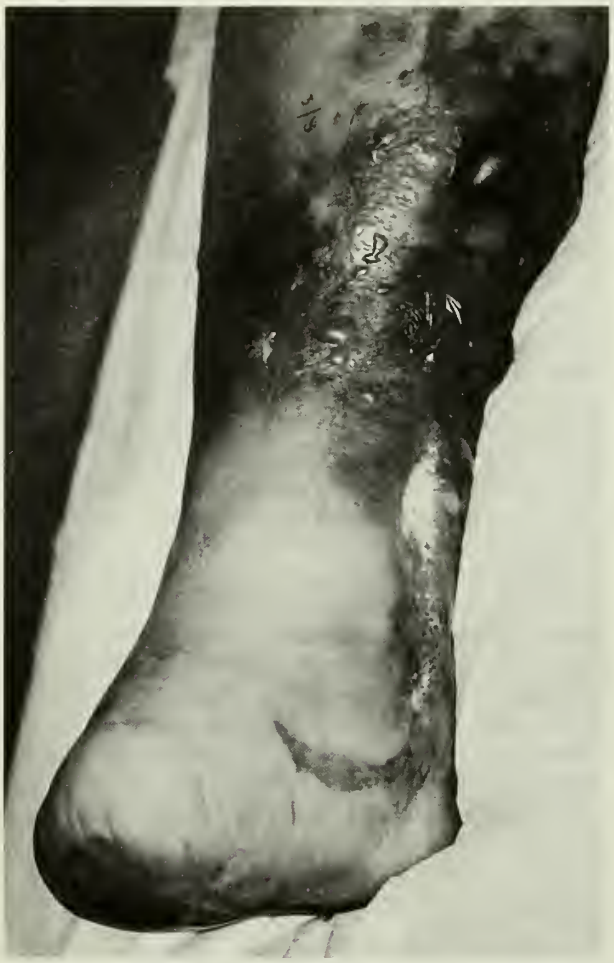

Figure 1.—The right lower extremity is shown. On the second hospital day, its color had changed to a deep red with a faint blue hue, and several discrete, black, necrotic bullae had erupted.

made. Cultures of two blood specimens drawn at the time of admission were reported to be growing oxidase-positive, gram-negative rods, and the antibiotic regimen was changed to the combination of imipenem and cilastatin sodium, plus gentamicin sulfate and clindamycin hydrochloride. An orthopedic surgeon (J.D.) was emergently consulted and immediately performed a below-the-knee amputation.

The postoperative course was eventful for disseminated intravascular coagulation and severe blood loss requiring 22 units of packed red cells, 20 units of fresh frozen plasma, and 18 units of platelets in the first 24 hours. The initial blood and surgical wound isolates were identified as *Vibrio cholerae* non-O1. This organism was also identified in a plantar wound culture, although not in pure culture. Other isolates included *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterococcus* species.

During the following week, the patient remained in critical condition and required multiple debridements. Cultures of wound specimens of healthy-appearing tissue from the first two debridements remained positive for *V cholerae* non-O1. On hospital day 9, the wound became more painful and developed a foul odor. At surgery, a knee disarticulation was necessary due to ascending subcutaneous necrosis. In the next few days, the patient's condition finally became stable, and he was able to provide the history of exposure of his plantar ulcer to sand at the bathhouse the night before admission. Investigation from the public health department discovered that this was untreated local sand that the proprietors had discarded before specimens could be obtained for culture. The patient was discharged on hospital day 22.

Discussion

It is not well known to the medical community that cholera and noncholera *Vibrio* strains are present in the western United States coastal regions. Further, these organisms are not generally recognized as pathogens that can be acquired in California. Our case is one of two San Diego County cases of waterborne non-O1 *Vibrio cholerae* disease identified by the Department of Public Health. *Vibrio cholerae* strains are found in several areas of the world, including the United States.[3,6,7] All *V cholerae* are similar with regard to structure, biochemistry, and ability to produce enterotoxins. They are oxidase-positive, gram-negative rods and are classified as O1 or non-O1 depending on whether they agglutinate in cholera polyvalent O1 antiserum; O1 organisms are agglutinated by antiserum, and non-O1 isolates are not.[8] More than 72 serotypes of *V cholerae* are classified as non-O1.[8]

The O1 strains typically cause the cholera epidemics in developing countries but do not cause disease outside the gastrointestinal tract. In contrast, non-O1 strains have been isolated from specimens of blood,[9-11] ear tract,[12] cellulitis,[13,14] cholecystitis,[15] and meningitis.[16] Fulminant *V cholerae* non-O1 necrotizing fasciitis has not been reported, however.

Infection from non-O1 *V cholerae* results from open wound exposure to infested sand or saltwater, estuary exposure, or from ingesting contaminated seafood. The pathogenic mechanism may reside partly in its ability to produce a number of extracellular toxins, including an enterotoxin similar to the cholera toxin,[17] cytolysins,[18] and a hemagglutinin or protease that is structurally, functionally, and immunologically similar to the elastase of *Pseudomonas aeruginosa*.[19] Further, established risk factors for non-O1 infection include immunocompromise, cirrhosis, or hematologic malignancy,[4,20,21] but the reasons for increased risk are not clear. Immunocompromised patients with human immunodeficiency virus (HIV) infection or a malignant neoplasm are more susceptible to bacterial infections from deficient cellular immunity. Patients with liver disease may have a defective chemotactic defense against infection.[22]

In conclusion, we report the first documented case of fulminant necrotizing fasciitis due to *Vibrio cholerae* non-O1. Our report describes an immunocompetent host (who tested negative for HIV during his hospital stay) with dia-

betes mellitus who has a history of many bacterial infections. The exposure of a chronic plantar ulcer to sand at a bathhouse infested with non-O1 *V cholerae* is the probable mechanism of entry that led to necrotizing fasciitis and septic shock. The history of pain out of proportion to physical findings suggested a deeper infection of the fascia that spread rapidly and resulted in septic shock. The inability to control necrotizing fasciitis despite surgical intervention often leads to amputation of extremities or death with involvement of abdominal or chest wall fascia. An aggressive medical-surgical team approach is necessary for the survival of the patient.

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Hyperammonemia With Severe Methanol Intoxication

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METHANOL POISONING leads to a well-described syndrome of metabolic acidosis with elevated anion gap and osmolar gap, vision impairment often leading to blindness, and in severe cases, progressive central nervous system dysfunction, renal and hepatic failure, and death.[1,2] The neurologic damage brought about by methanol poisoning, particularly that of the vision system, has been ascribed to the effects of formic acid, the principal toxic metabolite of methanol. Hyperammonemia, to our knowledge, has not been reported as a presenting feature of methanol toxicity. We report a case of severe methanol poisoning associated with hyperammonemia in the presence of near-normal liver function test results.

Report of a Case

The patient, a previously healthy 16-year-old boy, presented to the emergency department with symptoms of impaired vision and stupor. Two nights before admission, according to his family, the patient had been out drinking with friends. Subsequent investigation revealed that he had ingested methanol intended for use as a cleaning solvent but unaccountably stored in a vodka bottle. On the day before admission, the patient felt ill and vomited several times, but ascribed his symptoms to a hangover. On the day of admission, he was too ill to attend school and continued to have nausea and vomiting. While watching television that evening, he complained that he "couldn't see" and became progressively somnolent. On arrival at the emergency department, he was able to stand with assistance, but within moments of arrival became obtunded and had an apparent seizure. An endotracheal tube was inserted and supportive care begun.

The patient's initial vital signs included a blood pressure of 169/125 mm of mercury and a heart rate of 100 beats per minute. Arterial blood gas measurements with the patient receiving bag ventilation with 100% oxygen revealed a pH of 6.84, a P_{CO_2} of 19 mm of mercury, a P_{O_2} of 456 mm of mercury, and a calculated base excess of −31.3 mEq per liter. Diazepam and phenytoin were given to prevent further seizures. Administering

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
LDH = lactate dehydrogenase

intravenous naloxone hydrochloride and a solution of 50% dextrose in water produced no improvement in his mental state. The combination of severe metabolic acidosis, disturbed vision, and coma strongly suggested a diagnosis of methanol toxicity, and empiric therapy, including fluid resuscitation, ethanol infusion, and sodium bicarbonate infusion, was instituted. Pending the results of toxicology screens, the patient also received intravenous ceftriaxone sodium and acyclovir. Serum and urine toxicology screens were negative for ethanol, opiates, acetaminophen, salicylates, barbiturates, cocaine, and benzodiazepines.

The patient's serum methanol concentration on admission was 35 mmol per liter (113 mg per dl). A complete blood count was remarkable for a leukocyte count of 21.4×10^9 per liter (21,390 per mm^3), a hematocrit of 0.58 (58%), and a platelet count of 467×10^9 per liter (467,000 per mm^3). A blood chemistry profile gave the following values: sodium, 138, potassium, 4.7, and chloride, 97 mmol per liter; carbon dioxide, 4 mmol per liter; blood urea nitrogen, 6.8 mmol per liter (19 mg per dl); creatinine, 141 mmol per liter (1.6 mg per dl); and glucose, 14.3 mmol per liter (258 mg per dl). A serum lactate level was 11.2 mmol per liter. Liver function tests elicited the following values: aspartate aminotransferase (AST), 18 U per liter; alanine aminotransferase (ALT), 18 U per liter, γ-glutamyl transferase, 11 U per liter; lactate dehydrogenase (LDH), 181 U per liter; and alkaline phosphatase, 141 U per liter. Serum osmolality was 367 mOsm per kg (normal range, 278 to 305). Urinalysis revealed a specific gravity reported as "greater than 1.030" but was otherwise normal. A serum ammonia level, fortuitously measured on admission to rule out hepatic encephalopathy, was 347 μmol per liter (normal range, 7 to 27).

Hemodialysis was instituted on the night of admission. Despite aggressive supportive and specific therapy, the patient's hospital course was one of continued deterioration of multiple organ systems. The patient remained comatose; no further seizures were noted. Metabolic acidosis persisted despite dialysis and continued sodium bicarbonate infusion. The serum creatinine level rose to 230 mmol per liter (2.6 mg per dl) within 24 hours of admission and reached 504 mmol per liter (5.7 mg per dl) by the fourth hospital day. Profound hypokalemia developed, with serum potassium values remaining around 1.5 to 2.5 mmol per liter despite massive repletion. Coagulopathy developed, with prothrombin times increasing from 16.2 to 20.3 seconds and partial thromboplastin times from 39.9 to 56.1 seconds over the first 24 hours. Coagulopathy persisted despite replacement therapy. By the fourth day, the serum AST level had risen from 18 to 270 U per liter, the ALT level from 12 to 81 U per liter, and the LDH value from 181 to 1,418 U per liter.

When initially intubated, the patient demonstrated remarkable hyperventilation, with spontaneous minute ventilation often exceeding 40 liters per minute; yet, within six hours complete ventilatory support was necessary. Hemodynamic instability developed on the night of admission, with the patient becoming severely hypotensive (blood pressure, 60/30 mm of mercury) despite the administration of massive amounts of crystalloid and colloid solutions and the infusion of dopamine. A pulmonary artery catheter was placed, and the pulmonary capillary wedge pressure was maintained in the range of 10 to 16 mm of mercury. An echocardiogram revealed a small pericardial effusion and normal ventricular function. Additional infusions of phenylephrine hydrochloride, epinephrine, and norepinephrine bitartrate were required to maintain a systolic blood pressure of 80 to 90 mm of mercury. Serum ammonia levels were 55 and 63 mmol per liter on the second and third hospital days, respectively. By the fourth hospital day, the patient's condition had deteriorated to the point where meaningful recovery was deemed impossible. With the family's consent, life support was withdrawn, and the patient died.

Discussion

This unfortunate patient had a clinical course characteristic of severe methanol poisoning. An unusual feature of this case was a greatly elevated serum ammonia level on admission. Hyperammonemia persisted for at least two days despite hemodialysis, indicating an ongoing impairment of ammonia clearance. It is particularly interesting that the high initial ammonia level was found well before the development of catastrophic hepatic and renal failure.

Ammonia is a highly toxic by-product of amino acid catabolism and is normally cleared rapidly by its incorporation into urea.[3] Hyperammonemia results from either increased protein breakdown or impaired ureagenesis. In clinical practice, it is seen most often in patients with cirrhosis, especially in those with gastrointestinal bleeding. It is also a feature of Reye's syndrome. The diagnosis of Reye's syndrome was considered in this case, but was rejected on several grounds: there was no history of an antecedent viral illness; toxicology screens were negative for salicylates; there was no increase in serum aminotransferase levels until the third hospital day, as opposed to the early massive increase seen in Reye's syndrome; and the patient was hyperglycemic on admission, whereas normoglycemia or hypoglycemia is typical of Reye's syndrome.[4] Rhabdomyolysis, which has been reported as a complication of methanol poisoning (albeit without mention of hyperammonemia),[5] is a possible source of excess ammonia through the breakdown of muscle protein. Although specific evidence for rhabdomyolysis, such as serum creatine kinase measurement, was not sought, the absence of a positive hemoglobin test on the initial urinalysis makes substantial myoglobinuria unlikely.

Genetic defects involving enzymes of the urea cycle, such as ornithine transcarbamoylase or carbamoylphosphate synthetase, are possible causes of hyperammonemia.[3] These defects, however, present distinctive clinical syndromes in the neonatal period and are unlikely diagnoses in an otherwise healthy 16-year-old.

Interestingly, hyperammonemia with normal liver function is a frequent feature of several genetic syndromes involving errors of amino acid metabolism, grouped under the heading of "organic acidemias."[3,6,7] Examples include propionic, isovaleric, and methylmalonic acidemias. Hyperammonemia develops in these patients with organic acidemias even though all the enzymes of the urea cycle are present in normal amounts and function normally in vitro. There is experimental evidence that high levels of these organic acids,[8,9] or their coenzyme A esters,[10] can severely inhibit the conversion of ammonia into urea. Specifically, there is a decrease in the production of *N*-acetylglutamate, an allosteric activator of carbamoylphosphate synthetase. Carbamoylphosphate synthetase catalyzes the crucial reaction by which ammonia enters the urea cycle; a decrease in the amount of its activator (*N*-acetylglutamate) leads to a buildup of ammonia.

Because methanol toxicity can be regarded as an acquired organic acidemia (that is, formic acidemia), we speculate that formic acid may exert an indirect effect on ammonia clearance similar to that of the organic acids mentioned earlier. We further suggest that hyperammonemia may be an important and hitherto unappreciated contributor to the profound impairment of the central nervous system seen in patients with methanol poisoning. We encourage the early measurement of serum ammonia levels in suspected or confirmed cases of methanol toxicity, to help determine if this represents an isolated incident or a consistent feature of this disorder.

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MELAS Syndrome

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MELAS IS THE SYNDROME OF *m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes.[1] It is one of a number of mitochondrial syndromes that share the common characteristics of encephalopathy and myopathy. Other mitochondrial diseases include *m*yoclonus and *e*pilepsy with *r*agged *r*ed *f*ibers (MERRF),[2] Kearns-Sayre syndrome,[3,4] and progressive external ophthalmoplegia.[5] In recent years these syndromes have been shown to be associated with specific mutations of mitochondrial DNA (mtDNA).[6-10] At the same time, more common conditions such as cardiomyopathy, aminoglycoside-induced ototoxicity, and some forms of diabetes mellitus also have been shown to be associated with mitochondrial DNA mutations.[11-19] These associations, and the recognition of "incomplete" forms of the above encephalopathic and myopathic syndromes, indicate that mitochondrial dysfunction may be underrecognized in the pathogenesis of a number of diseases.

We report the case of a patient with the MELAS syndrome. We use the case as a basis for discussing the current clinical and molecular understanding of the syndrome and to explore the probable role of mitochondrial mutations in other diseases.

Report of a Case

A 43-year-old woman presented to the emergency department in respiratory arrest after five tonic-clonic seizures. She had had lethargy with nausea, vomiting, and diarrhea for a week and slurred speech for two days before admission. The patient's husband reported that she had been healthy with the exception of exercise intolerance and hearing loss since childhood. Her family history was relevant for at least ten maternally related family members with some combination of hearing loss, small stature, and adult-onset diabetes mellitus. On physical examination she appeared ill, was of slight build, and was being sustained by mechanical ventilation. Her blood pressure was 80/50 mm of mercury, her heart rate 100 beats per minute, respiratory rate 24 breaths per minute, and temperature 38.1°C (100.6°F). She was unresponsive even to deep pain, and her lungs had bibasilar crackles.

Laboratory evaluation showed an arterial pH of 7.20;

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a serum lactate level of 0.62 mmol per liter (0.62 mEq per liter; normal, 0.5 to 2.2 mmol per liter); serum bicarbonate, 12 mmol per liter (12 mEq per liter; normal, 23 to 29); and serum glucose, 10.0 mmol per liter (180 mg per dl; normal, 3.8 to 6.4 mmol per liter). An echocardiogram showed global hypokinesis with an ejection fraction estimated at 20%, and magnetic resonance imaging of the brain showed a left parietotemporal infarct, diffuse cerebral atrophy, and bilateral basal ganglial calcifications.

The patient was suffering from multisystem failure, the cause of which was not clear. A MEDLINE search was done using the keywords "deafness," "diabetes mellitus," and "myocardial disease." A single reference was recovered implicating mitochondrial disease as the basis for such a syndrome.[13] This led to a presumptive diagnosis of the MELAS syndrome, which was later confirmed by a muscle biopsy showing ragged red fibers and DNA testing that revealed the characteristic mitochondrial DNA mutation of the MELAS syndrome.

Discussion

In 1975 a syndrome consisting of lactic acidosis and mitochondrial myopathy was described in two separate reports.[20,21] The acronym MELAS was proposed for the syndrome in 1984.[1] In a review in 1992, the diagnostic criteria were clarified using 69 cases.[22] It was proposed that the syndrome should be suspected by the presence of three invariant criteria: strokelike episodes before age 40; encephalopathy characterized by seizures, dementia, or both; and either ragged red fibers on muscle biopsy or the presence of lactic acidosis, or both. It was further proposed that the diagnosis could be considered secure if any two of normal early development, recurrent headache, and recurrent vomiting also were present. The same year, 40 different cases of MELAS were reported.[23] Both studies noted the presence of the above-named characteristics plus exercise intolerance, muscle weakness, and computed tomographic scan abnormalities—low-density areas, cortical atrophy, basal ganglia calcifications—in greater than 80% of cases. Other clinical signs have been noted, including short stature, hearing loss, positive family history, and cardiomyopathy.

More than 80% of the patients with the MELAS syndrome who have undergone genetic testing have been shown to carry a specific point mutation of mtDNA—an adenine to guanine transition at position 3243 of the mitochondrial genome.[23,24] This mutation lies within the DNA coding for the transfer RNA specific for leucine.[6] It is hypothesized that the mtDNA mutation causes a generalized impairment of protein translation that leads to defects of multiple respiratory chain enzymes. This disruption of aerobic metabolism would result in the clinical manifestations of the syndrome.[23]

The MELAS syndrome is acquired only through maternal transmission because the ovum supplies close to 100% of the mitochondria to the zygote. This pattern of inheritance can be confused with autosomal dominant inheritance, but is distinguished by the lack of paternal transmission of the trait. A thorough family history of our patient revealed a pattern of maternal inheritance for at least four preceding generations. Affected family members possessed any number of the following characteristics: deafness, small stature, diabetes mellitus, and exercise intolerance. Of these characteristics, deafness was the most pervasive and a critical clinical feature in reaching a unifying diagnosis. Our patient did have one child, a 14-year-old son, who was noted to be of small stature but had yet to demonstrate any other signs or symptoms of MELAS.

It should be noted that the mtDNA mutation is not found in all the mitochondria of an afflicted person. There exists a mixture of normal and mutant mtDNAs within a single cell—a condition called heteroplasmy.[6,24] The percentage of mutant mtDNA within different tissues also varies.[22,25] These findings might account for the variety of clinical manifestations seen in persons with the MELAS syndrome. Furthermore, asymptomatic or oligosymptomatic relatives of MELAS patients have been shown to have mutant mtDNA, but in levels proportional to the severity of their disease.[24] This adds to the evidence that the mutation plays a direct role in the pathogenesis of the syndrome.

Overall morbidity and mortality data for the MELAS syndrome are not known. Likewise, there is no known definitive therapy for the syndrome. A case has been reported of a MELAS patient who was successfully treated with riboflavin and niacinamide (nicotinamide)—precursors of coenzymes in the mitochondrial electron transport chain.[26] The patient presented here was treated supportively during her prolonged hospital stay, as well as empirically with the administration of niacinamide and riboflavin. She had a slow but progressive return to her previous functional status, and after nine months her symptoms had not recurred.

The MELAS syndrome is one of a number of known mitochondrial syndromes. As with MELAS, most of these syndromes are associated with specific nucleic acid mutations. MERRF is a syndrome characterized by myoclonus, epilepsy, ataxia, and ragged red fibers on muscle biopsy. It is associated with a specific transfer RNA point mutation.[7] Similarly, Leber's hereditary optic neuropathy—a syndrome of central optic nerve death, blindness, and cardiac dysrhythmia—and a syndrome of ataxia, retinitis pigmentosa, and peripheral neuropathy are associated with point mutations within respiratory complex genes of mitochondria.[11] Two other syndromes, progressive external ophthalmoplegia and a syndrome of ophthalmoplegia, pigmentary retinopathy, heart block, and cerebellar ataxia known as Kearns-Sayre syndrome, have been associated with large deletions in mtDNA.[10] These mitochondrial syndromes illustrate the broad spectrum of disease caused by mutations in mtDNA.

There is a relationship between mtDNA abnormalities and disease states other than encephalomyopathies (such as MELAS). A report in 1992 demonstrated an excess of maternal transmission of non–insulin-dependent diabetes mellitus, whereas several other studies have associated

some forms of diabetes with specific mtDNA mutations.[12,13,18] Furthermore, an mtDNA point mutation has been associated with a syndrome of adult-onset myopathy and cardiomyopathy,[11] and recent data have demonstrated an mtDNA mutation that confers susceptibility to aminoglycoside ototoxicity.[14-16] This information represents a rapid increase in the recognition and understanding of mitochondrial disease and should serve to sensitize clinicians to patterns of maternal inheritance, particularly in patients with multisystem disease. Furthermore, they suggest a role for mtDNA defects in more common disorders.

The current understanding of the MELAS syndrome and other diseases related to mtDNA mutations is a result of recent advances in molecular biology and molecular diagnostic techniques. A number of diseases were discussed in a recent editorial—including those caused by mutations in mtDNA—that now have been introduced into the realm of adult medicine as a result of advances in medical science.[27] These range from conditions such as cystic fibrosis and phenylketonuria, in which early recognition and management have allowed survival well into adulthood, to adult-onset genetic disorders such as the mitochondrial encephalomyopathies. The editorial writers called for internists—and we would include all practitioners of adult medicine—to assume increased responsibility for the diagnosis and management of this expanding number of disorders. This case report serves to emphasize the need for greater recognition and understanding of disorders related to mitochondrial dysfunction (as well as the growing number of "new" adult diseases) and illustrates one strategy for dealing with the need for an ever-expanding knowledge base—the use of computer-based information systems.

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Topics in Primary Care Medicine

Inherited Liver Diseases in Adults

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Important inherited disorders causing acute and chronic liver disease include hemochromatosis, Wilson's disease, α_1-antiprotease (antitrypsin) deficiency, and cystic fibrosis. The detection of an index case has implications for screening family members. A normal life span can be expected with treatment in asymptomatic patients with Wilson's disease and hemochromatosis. We present a clinical approach to disease recognition, investigation, and screening.

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Inherited disorders have been increasingly recognized as a cause of acute and chronic liver diseases. Common or important disorders of adults include hemochromatosis, Wilson's disease, α_1-antiprotease (antitrypsin) deficiency, and cystic fibrosis. Their typical manifestations outside the hepatobiliary system should alert astute clinicians. Establishing the diagnosis is not difficult in most cases. If the diagnosis of hemochromatosis or Wilson's disease is confirmed, asymptomatic persons should have a normal life span with appropriate treatment.

Hemochromatosis

Hemochromatosis is an iron storage disorder in which excessive deposition of iron occurs within parenchymal cells of many organs, resulting in varying degrees of functional impairment.[1] The condition can be genetically acquired and is then called genetic or hereditary hemochromatosis. Iron overload with secondary tissue injury occurs in a number of other disorders, usually associated with anemia of ineffective erythropoiesis, and is called acquired or secondary hemochromatosis. Only hereditary hemochromatosis will be discussed here. It is one of the most common inherited disorders in whites, with a gene frequency estimated to be about 5%. About 1 in 400 whites is homozygous and at risk for the development of the clinical syndrome.[2] The gene is located on the short arm of chromosome 6, near HLA class IA and F loci, and is often associated with the HLA-A3 genotype.[3]

In hereditary hemochromatosis, there is increased net iron absorption in the context of normal dietary intake and normal levels of erythropoiesis. Some evidence suggests an increase in the rate constant for the transfer of mucosal iron to the plasma, but the nature of the defect has not been clearly explicated.[4]

The disease pursues an insidious course, often presenting in the fifth decade or later, although symptoms may occur as early as the second decade. Men are five times more frequently affected than women, probably due to a slower rate of iron accretion in the latter.[1] Also, the onset is often earlier in men. The initial symptoms are nonspecific and may thus delay diagnosis. Common initial complaints are lethargy, weakness, abdominal pain, loss of libido or impotence, change in skin color, and symptoms related to the development of diabetes mellitus. Hepatomegaly is detected in more than 80% of patients, and this may exist in the absence of symptoms or functional impairment of the liver. Manifestations of cirrhosis and portal hypertension, including jaundice, spider angiomas, and gynecomastia, can be seen. Hepatocellular carcinoma develops in about 30% of patients who have cirrhosis. Excessive skin pigmentation (bronze or slate-gray) due to melanin deposition is common in advanced cases. About two thirds of patients have diabetes mellitus. Arthropathy caused by the deposition of hemosiderin and calcium pyrophosphate crystals in synovial lining cells is symmetrical, involves small and large joints, and can precede other manifestations. Cardiomyopathy occurs in about 10% of patients, presenting as heart failure or arrhythmias. In early adulthood, the disease may occur as hypogonadism of pituitary origin. It should be noted that all of these symptoms and signs may be absent when the disease is detected during a routine checkup, the management of an incidental illness, or family screening.

Hemochromatosis should be ruled out in first-degree relatives of a known proband or in any white patient with unexplained hepatomegaly, idiopathic cardiomyopathy, loss of libido, abnormal skin pigmentation, diabetes mellitus, arthritis, or any combination thereof. The diagnosis is established by documenting iron overload. The evaluation begins with the measurement of transferrin-iron saturation (derived from the serum iron level and iron-binding capacity) and the serum ferritin level. It has been recently suggested that, in a fasting blood specimen, a transferrin saturation of 60% in men and 50% in women should raise a suspicion of hemochromatosis and lead to the measurement of the serum ferritin level.[5] Any patient with an isolated elevated transferrin saturation should be observed, measuring saturation and

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ferritin levels every two years, and monitoring for a rise in the serum ferritin level.[1] If the serum ferritin value is abnormal, a liver biopsy should be done. It can provide both qualitative (using the Perls' Prussian blue test) and quantitative estimation of tissue iron and an assessment of the extent of tissue damage. A hepatic iron index—hepatic iron in micromoles per gram of dry weight divided by age in years—of 2 or more is thought to reliably distinguish homozygous hereditary hemochromatosis from the heterozygous state and other liver diseases.

On occasion, it may still not be possible to distinguish hereditary hemochromatosis from the heterozygous form and secondary iron overload. In exceptional circumstances, physicians may have to use venesection therapy to differentiate these states. In patients with hereditary hemochromatosis, it takes many months of weekly phlebotomy to clear the large iron load, whereas in patients with other conditions, it generally takes only a few months to produce iron deficiency and anemia.

Once the diagnosis of hereditary hemochromatosis is established, it is extremely important to screen all first-degree relatives, including children, because mating between a homozygote and a heterozygote may have occurred. Should these screening tests be negative, measuring transferrin saturation and serum ferritin levels at five-year intervals is appropriate for offspring or young relatives of an affected person. Screening of the general population for hereditary hemochromatosis appears to be cost-effective, but it is not widely practiced.[6] It may be reasonable to measure the transferrin saturation in screening serum chemistry profiles.

Treatment consists of removing excess body iron by whole-blood phlebotomy, coupled with the support of damaged organs. Most patients tolerate 500-ml phlebotomies done once or twice each week. Such weekly phlebotomy is usually required for two to three years. There is general abatement of all symptoms and signs, except arthritis and hypogonadism. Once initial iron depletion is accomplished, as confirmed by the presence of slight anemia and a decrease in the transferrin saturation to 45% and serum ferritin levels to 50 μg per liter (50 ng per ml) or lower, lifelong maintenance phlebotomy therapy is commenced. Most patients require venesection at intervals of two to six months. The serum ferritin level should be measured yearly to estimate body iron stores. Because alcoholism adversely affects the prognosis of this condition, it is prudent to recommend that patients abstain from excessive intake of alcohol. Pharmacologic doses of vitamin C should also be prohibited. Life expectancy in symptomatic patients is extended considerably with phlebotomy therapy; in the absence of cirrhosis, it can be restored to normal. Those with cirrhosis or hepatic fibrosis have a 200-fold increased risk over a matched normal population of hepatocellular carcinoma developing and require surveillance by periodic liver ultrasonography and measurements of serum α-fetoprotein levels.

Wilson's Disease

Wilson's disease (hepatolenticular degeneration), an autosomal recessive disorder of copper transport, is characterized by the accumulation of copper in the liver and secondarily in the brain, corneas, and kidneys. The gene for Wilson's disease has been mapped to chromosome 13 at the q14.3 region.[7] The gene frequency is 1 in 180, and there is an approximate homozygote prevalence of 1 in 30,000. The Wilson's disease gene encodes for a homologous cation transporting P-type adenosine triphosphatase protein, most likely involved in copper transport and predominantly found in liver, kidneys, and placenta. Serum ceruloplasmin levels are usually, but not always, markedly reduced in patients with Wilson's disease. The primary defect does not appear to be directly related to this protein as the gene for ceruloplasmin is on chromosome 3. Also, patients are occasionally seen who have normal serum ceruloplasmin levels and some heterozygotes in whom Wilson's disease never develops who can have reduced levels.[8] The underlying biochemical defect is not fully explicated, but copper accumulation appears to be caused by decreased transport of copper into bile. How the nonfunctioning Wilson's disease gene leads to this decrease is not yet known.[9]

The onset of Wilson's disease after 40 years of age is rare, although cases have been described of patients presenting in the fifth and sixth decades. The initial clinical manifestations are hepatic, neurologic, or psychiatric, with occasionally a hematologic, renal, or endocrine presentation. Sibling screening can identify asymptomatic affected persons. Hepatic involvement encompasses a broad spectrum of acute and chronic liver diseases. The course is most commonly long term, characterized by signs of postnecrotic cirrhosis or chronic active hepatitis with no specific distinguishing features. In a few patients, Wilson's disease can present as fulminant hepatic failure or acute hepatitis. The presence of hemolytic anemia associated with liver disease should prompt a clinician to consider Wilson's disease.[10] Neurologic manifestations commonly appear in adolescence or early adulthood and include dysarthria, movement disorders, ataxia, and micrographia. An adolescent may have deteriorating performance in school or athletics. Psychiatric symptoms have been underemphasized, and Wilson's disease should be considered in any young patient with newly occurring psychiatric illness, including an inability to cope, labile moods, depression, and outright psychosis.[11] Kayser-Fleischer (KF) rings, located at the periphery of the cornea, consist of dense granules of copper and sulfur and are green-yellow or brown. When present with neurologic disorders, KF rings establish the diagnosis of Wilson's disease. The absence of these rings, however, does not exclude the disease. Abnormalities of renal tubular function, Coombs'-negative nonspherocytic hemolytic anemia, arthritis or arthralgia, and amenorrhea can also occur.

This disease should be considered in any person younger than 40 years with a neurologic disorder of

undetermined cause, chronic active hepatitis or cirrhosis, unexplained persistent elevation of serum aminotransferase levels, acute hepatitis or fulminant hepatic failure, or hemolytic anemia. The diagnosis is confirmed when a serum ceruloplasmin concentration of less than 200 mg per liter (20 mg per dl) is associated with either the presence of KF rings on slit-lamp examination or a hepatic copper concentration of greater than 250 μg per gram of dry weight.[12] Symptomatic patients also excrete more than 1.6 μmol (>100 μg) of copper per day in the urine and show histologic and qualitative (using orcein staining) abnormalities on liver biopsy. Note that special handling of liver specimens is needed to obtain accurate quantitative measurements of the hepatic copper concentration. Siblings of a proband with Wilson's disease should be screened. A normal serum ceruloplasmin level and normal 24-hour urine copper levels (in sibs 15 years of age or older) makes the diagnosis unlikely.[11]

Therapy with chelating agents should be instituted as rapidly as possible after the diagnosis is made and continued throughout life, including during pregnancies. Lifelong compliance is absolutely essential; inadvertent discontinuation of chelation therapy has resulted in hepatic decompensation and death. Many clinicians think that penicillamine is the drug of choice. Trientine hydrochloride can be used as an alternative initial decoppering agent in patients with penicillamine allergy. Some think that the use of oral zinc is as efficacious as penicillamine in maintenance therapy.[11] Several recent reviews give details of drug therapy.[8,10-12] The prognosis is excellent, with the reversal of all features, except in advanced cases. In patients with fulminant hepatic failure due to acute wilsonian hepatitis or advanced cirrhosis, liver transplantation may be necessary.[13] This is an attractive option because it also corrects the metabolic defect in the liver, making further specific therapy for Wilson's disease unnecessary.

α_1-Antiprotease Deficiency

α_1-Antiprotease (antitrypsin) functions to protect tissues from proteases such as neutrophil elastase. The phenotype of α_1-antiprotease is inherited and reflects the expression of codominant alleles on the long arm of chromosome 14 that control the electrophoretic mobility of the protein. The phenotype *PiMM* (Pi for protease inhibitor), which is present in 95% of this country's population, is associated with normal serum levels of α_1-antiprotease. The homozygous *PiZZ* phenotype is accompanied by severe deficiency, whereas the *PiMZ* phenotype causes intermediate deficiency. In northern European descendants, the *PiZ* gene has a frequency of 1% to 2%, and there is a homozygote prevalence of 1 in 2,000 to 1 in 6,700.[14] Of more than 70 allelic variants known, only the Z allele and some of rare M variants have been reported to be associated with liver disease.

α_1-Antiprotease deficiency primarily predisposes children to liver disease and adults to emphysema and to liver disease. It is the deficiency in the serum of α_1-antiprotease that leads to lung disease. In contrast, the liver disease relates to the presence of the abnormal Z protein in the liver, not to the serum level of α_1-antiprotease. Thus, liver disease can occur not only in deficient persons (*PiZZ*), but also in persons heterozygous for the Z allele (for example, *PiMZ*) who do not have α_1-antiprotease deficiency in the serum. In nearly 80% to 90% of *PiZZ* persons, liver disease does not develop, despite the low serum levels and the aggregation of abnormal α_1-antiprotease in hepatocytes. Why only a small number of these persons is affected is not clear. A recent report has suggested that there is a lag in intracellular degradation of mutant protein in *PiZZ* homozygotes in whom liver disease does develop.[15] In the neonatal period, α_1-antiprotease deficiency-related liver disease presents with cholestasis or acute hepatitis that usually resolves. Liver disease in adults can present at any age. α_1-Antiprotease deficiency should be ruled out in any patient with hepatitis of unknown cause, chronic active hepatitis, or cryptogenic cirrhosis and in adults with the early onset of pulmonary emphysema. There is an increased incidence of hepatocellular carcinoma of as much as 20-fold in this condition.

The deficiency state can be suggested by directly inspecting the serum protein electrophoresis or its densitometer tracing and confirmed by measuring the α_1-antiprotease level. A definitive diagnosis must be made by phenotyping. A liver biopsy will show diastase-resistant deposits positive for periodic acid-Schiff stain in periportal hepatocytes of persons with the *PiZ* phenotype, regardless of whether or not they have liver disease. Medical therapy is largely supportive. Subjects identified to have the *PiZ* phenotype should be instructed to avoid smoking. Infusions of α_1-antiprotease derived from pooled plasma or obtained by recombinant DNA methods are under investigation for the treatment of pulmonary disease. *MZ* heterozygotes have an increased, albeit small, risk of liver disease developing and should have liver biochemistry tests checked at one- to two-year intervals. Advanced liver disease requires liver transplantation. The recipient assumes the Pi phenotype of the donor.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder in which defective salt and water transport in epithelial tissues results in the dysfunction of various organs, including the lungs, pancreas, and liver. It is caused by one of several mutations in a gene located on chromosome 7 that codes for the cystic fibrosis transmembrane conductance regulator. Homozygous frequency is 1 in 2,500 in whites and 1 in 17,000 in African Americans. With the recent extended life expectancies for affected persons, hepatobiliary abnormalities are being seen in as much as 50% of patients.[16]

Cholestasis can occur in the newborn period. Symptomatic liver disease has been reported in 2% to 16% of children or young adults with cystic fibrosis. Focal biliary or multilobular cirrhosis is typical of this

disorder. Cirrhosis is ascribed to the accumulation of inspissated mucus in intrahepatic ducts, producing an inflammatory response and fibrosis. Fatty liver, biliary sludge, cholelithiasis, sclerosing cholangitis, and microgallbladder can occur. It is useful to note that hepatic disease can be silent, and the first presentation may be portal hypertension.

Because it is often subclinical, it is difficult to detect liver disease in patients with cystic fibrosis. Liver test abnormalities can be intermittent, and focal histologic lesions can lead to biopsy sampling error. Elevated serum alkaline phosphatase levels of hepatic origin can be an early indicator. In appropriate settings, an assessment of hepatic function or clearance or imaging can help. Children and young adults with unexplained portal hypertension should have the sweat chloride and sodium concentrations measured, which are reliably elevated in persons with cystic fibrosis.[17]

Bile acid therapy for the cholestasis of cystic fibrosis has shown promise in preliminary studies, but its use is not yet routinely recommended.[18] Similarly, the value of supplemental taurine remains to be investigated. Successful liver transplantation has been done for advanced hepatic disease. The favored strategy for gene therapy is to use viral DNA as carrier molecules (viral vectors) into which the gene sequence of interest has been incorporated to allow its introduction and expression in host cells. A phase 1 trial of gene therapy for cystic fibrosis lung disease using E_1-deleted adenovirus has been now reported.[19] Although such therapy may be useful for the pulmonary disease, unfortunately, it will not affect hepatic or pancreatic dysfunction.

Clinical Approach

The presentations and diagnostic tests for these four disorders are summarized in Table 1. Once considered, a diagnosis is not difficult to confirm in most patients; therefore, a high index of suspicion is required. In general, no one laboratory test is pathognomonic, and the diagnosis is established by a combination of tests in appropriate persons.

In acute hepatitis or fulminant hepatic failure, Wilson's disease should be considered once viral causes have been excluded. Evidence of hemolysis should prompt a clinician to consider Wilson's disease. In any patient with persistent abnormalities of liver function,

TABLE 1.—*Presentations and Tests for Inherited Diseases*

Disorder	*Presentations*	*Tests**
Hemochromatosis	Asymptomatic liver test abnormalities Cirrhosis Diabetes mellitus Arthritis Skin pigmentation Abdominal pain Weakness and fatigue Cardiomyopathy Testicular atrophy Hepatocellular carcinoma	Transferrin saturation Serum ferritin level Liver biopsy Hepatic iron index
Wilson's disease	Asymptomatic liver test abnormalities Acute hepatitis Fulminant hepatic failure Chronic active hepatitis Cirrhosis Kayser-Fleischer rings Neurologic disorders Renal tubular acidosis Psychiatric disorders	Serum ceruloplasmin level Slit-lamp examination Quantitative hepatic copper 24-Hour urine copper
α_1-Antiprotease deficiency	Neonatal hepatitis Pulmonary emphysema Chronic active hepatitis Cirrhosis Hepatocellular carcinoma	Serum protein electrophoresis Serum α_1-antiprotease levels Pi phenotyping Liver biopsy
Cystic fibrosis	Cirrhosis Fatty liver Cholelithiasis Sclerosing cholangitis Cholangiocarcinoma Biliary strictures Pancreatic insufficiency Pulmonary disease Infertility	Sweat chloride test Liver biopsy

*Diagnosis is established not by a single but by a combination of abnormal test results. See text for details.

cirrhosis, or portal hypertension, initial investigations should be directed toward excluding common causes such as viral hepatitis (including hepatitis B or C), alcoholism, and drugs. Once these have been excluded, screening should be done for inherited liver diseases. A histologic picture of chronic active hepatitis can be seen in patients with Wilson's disease and α_1-antiprotease deficiency. For patients with "cryptogenic" cirrhosis, physicians must ensure that all causes, including inherited liver disease, have been excluded. Patients with cirrhosis from inherited liver diseases, especially hemochromatosis and α_1-antiprotease deficiency, have increased risk of hepatocellular carcinoma and need to be closely observed by serial ultrasonograms and serum α_1-fetoprotein measurements. The optimal frequency of these screening tests has not been established. Japanese investigators report some advantage in doing these tests at three-month intervals with yearly abdominal computed tomographic scans. Unfortunately, hepatocellular carcinoma may be an initial presentation of cirrhosis from inherited liver diseases, and these diagnoses must be ruled out in any patient with hepatocellular carcinoma who lacks markers for hepatitis B or C.

Several limitations should be remembered regarding the interpretation of various laboratory tests. In the diagnosis of hemochromatosis, clinicians should realize that serum transferrin levels are also increased by oral contraceptive use and pregnancy. An increase in serum ferritin levels occurs in acute liver injury, including acute alcoholic liver disease, and acute illnesses, such as pneumonia. An elevated serum ferritin level should therefore be rechecked once the acute event has subsided. In the diagnosis of Wilson's disease, a serum ceruloplasmin value of less than 200 mg per liter in appropriate patients is suggestive. About 4% of homozygotes have normal ceruloplasmin levels, however, and as much as 20% of heterozygotes can have low levels. Reduced ceruloplasmin levels are also found in persons with hypoalbuminemia and Menkes' syndrome. The serum level of ceruloplasmin, like other acute-phase reactants, rises in response to pregnancy, estrogen therapy, and acute hepatitis and other inflammatory states. The diagnosis should be confirmed by quantitative liver copper determination. Serum α_1-antiprotease levels can also increase in patients with acute liver injury and acute inflammation.

Because the hemochromatosis gene is common, screening by measuring transferrin saturation in routine serum chemistry determinations is probably appropriate. This is appropriate even if patients have other liver disorders, such as alcoholism. All first-degree relatives (including children) of an index case of hemochromatosis should be screened. In Wilson's disease, all siblings should be screened. The prenatal diagnosis of cystic fibrosis using a DNA probe has been reported in research settings. In α_1-antiprotease deficiency, screening of family members can be offered, although its value is uncertain because the expression of the disease varies.

Psychological consequences of screening can be adverse, and genetic counseling is advisable. In Sweden, screening of newborns for α_1-antiprotease entailed severe adverse psychological consequences in more than half of the families, and these consequences were still evident five to seven years later.[20] Physicians should also consider the possible repercussions of the diagnosis of such genetic conditions, including the potential for discrimination by employers and insurance carriers.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
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Radiologic Case

A Case of Free Air in the Peritoneum

ROBERT LEE, MD; MOHAMMED ZAMAN, MD; ELLIOTT BONDI, MD; MRIDULA SAXENA, MD;
and HENRY ZUPNICK, MD, *Brooklyn, New York*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

The patient, a 42-year-old man, presented to the hospital with a fall and leg weakness due to human immunodeficiency virus-related radiculopathy. During the course of the hospital stay, the adult respiratory distress syndrome developed. An endotracheal tube was inserted; the patient removed the tube and had to be intubated a second time. After the second intubation, subcutaneous emphysema developed on his neck, face, arms, and anterior chest wall. There was no pneumothorax on a chest film. Two days later, another roentgenogram was taken.

What does the chest film show?

What are the different diagnostic possibilities?

How can the diagnosis be proved?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

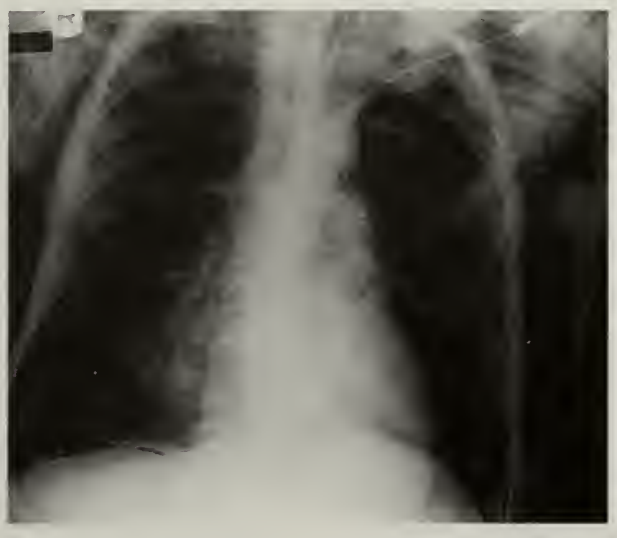

Figure 1.—An anteroposterior x-ray film of the chest was taken 2 days after the patient had a normal roentgenogram.

(Lee R, Zaman M, Bondi E, Saxena M, Zupnick H: A case of free air in the peritoneum. West J Med 1995; 163:387-388)

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ANSWER: Pneumoperitoneum due to barotrauma

THE ROENTGENOGRAM SHOWS free air under the right side of the diaphragm in addition to subcutaneous emphysema throughout the soft tissues. Usually the presence of free air under the diaphragm suggests a surgical emergency because it may represent an acute perforation of an abdominal viscus. Free air may also be found after laparotomy or laparoscopy. Perforation can be demonstrated by giving the patient an oral contrast medium and observing for any extravasation. This patient had a gastrografin study done that revealed no extravasation of the contrast agent into the peritoneum.[1]

The free air in this case was likely caused by barotrauma. Alveoli can rupture, and air can dissect along the peribronchial space or perivascular space. This air can then go to the mediastinum, subcutaneously, or beneath the visceral pleura, causing a pneumothorax.[2] If the air goes to the mediastinum, and the patient has an absent peritoneal pleura and a defect in the diaphragm such as a posterolateral (Bochdalek's) hernia, parasternal (Morgagni's) hernia, or the central opening of the diaphragm, then air can track downwards into the peritoneal cavity.[3]

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Editorials

The Value of the History and Physical for Shoulder Pain

ALTHOUGH SOPHISTICATED imaging techniques aid in the visualization of the musculoskeletal system, most disorders about the shoulder girdle can be diagnosed by a simple yet thorough history and physical examination.[1] High-powered investigative aids more often confirm an established diagnosis rather than identify an unknown primary diagnosis. The basic skills of the history and physical examination are often overlooked, placing an excessive dependence on technology. This becomes glaringly obvious as more patients present to the specialist's office with a magnetic resonance image (MRI) even before plain radiographs have been taken.

The key to the successful treatment of any shoulder problem is an accurate diagnosis. Several factors in the history play a major role in formulating the diagnosis and will therefore immediately guide a physician in the appropriate direction. Age, the chief complaint, and the mechanism of injury are invaluable in the diagnostic process. The history should be patterned so as to exclude the presence of referred pain, infection, or tumor. It is important to remember that the evaluation of the shoulder begins with the cervical spine because this is a common source of local referred pain and the symptom complexes of these two areas often overlap. Pain that is duplicated by range of motion or manipulation of the neck is of cervical origin despite the fact that it may be perceived about the shoulder. Pain of a radicular nature such as this often produces a pain-free examination of the shoulder. Hand dominance, occupation, and aggravating and alleviating factors are also of utmost importance. Because pain is the most common reason people seek medical attention, obtaining specific details regarding its nature, duration, and onset is helpful.

As in other areas of medicine, different orthopedic disorders afflict different age groups. The most common cause of anterior shoulder pain in those older than 40 years is impingement. Impingement is most commonly caused by narrowing of the outlet formed by the acromion, coracoacromial ligament, and the acromioclavicular joint, resulting in encroachment on the underlying rotator cuff tendons.[2] Typically patients will have pain on overhead elevation and internal rotation maneuvers, such as putting the arm in a shirt or coat sleeve or attempting to fasten a brassiere. The pain has an insidious onset, with exacerbation at night preventing or disturbing sleep. The findings of the physical examination are notable for pain with forced forward elevation (the Neer impingement sign) that is alleviated by the subacromial administration of lidocaine. Even before plain radiographs, we now have a confirmed diagnosis. Based on the duration of symptoms, the age of the patient, and failed previous methods, the decision can be made as to whether or not further diagnostic studies are warranted. Advanced imaging of the rotator cuff would therefore confirm an already established diagnosis of impingement, in addition to elaborating on the extent of cuff damage, such as tendinitis versus complete tendon tear, each of which often take different therapeutic paths.

Instability is the second most common symptom in the shoulder and tends to be a disease of the young as compared with those suffering from rotator cuff tears, whose average age is 55 to 60 years. The instability, traumatic or atraumatic, may be vague in its presentation or readily described as "slipping out of the joint." Patients have pain and an unsettling feeling most commonly with abduction and external rotation, such as in the cocking phase of throwing, indicative of anterior instability. Inferior and posterior instability are also seen, presenting with symptoms such as difficulty carrying packages at the side (inferior) or pushing through a revolving door with arms out in front (posterior). The findings of a physical examination are remarkable for apprehension or guarding in positions that stress the direction of instability. General ligamentous laxity may be present, but not necessarily so. A complete neurologic examination is warranted because of the possibility of associated nerve injury. The axillary nerve is most commonly involved, resulting in decreased sensation over the lateral upper arm with deltoid weakness. Again, the diagnosis is made before imaging. Plain radiographs can confirm the diagnosis by the presence of a Hill-Sachs or reverse Hill-Sachs lesion indicative of anterior or posterior instability, respectively. To visualize the glenohumeral articulation adequately, it is imperative that at least a trauma series, consisting of scapular anteroposterior (AP) and lateral views in addition to an axillary view, be taken. The axillary view is the single most important view to assess the articulation and to confirm dislocation and reduction.[3] Posterior dislocations are still missed in as many as 80% of cases at the initial evaluation, which is often a direct result of inadequate or absent axillary radiographs. Patients with this disorder present classically with the arm locked in internal rotation with an inability to abduct or externally rotate. It may have resulted from seizure, electrocution, direct trauma, or a fall onto an outstretched, forward-flexed arm. Whatever the cause, it is here that a complete set of radiographs plays a most vital role.

Arthritis about the shoulder girdle is primarily a disorder of an older population. A possible exception is that of acromioclavicular arthritis, which may be seen in younger patients who do heavy labor, those who carry objects on the shoulder such as carpenters, and weight lifters. Acromioclavicular inflammation or arthritis presents with a history of pain over the top of the shoulder, sometimes associated with swelling. On physical examination, pain is elicited on cross-chest adduction and internal rotation, both of which compress the joint. There is point tenderness over the acromioclavicular joint. This classic history and physical finding is essentially pathognomonic for acromioclavicular joint disorder. Plain acromioclavicular

joint and axillary radiographs can confirm joint narrowing, osteophytes, or distal clavicular resorption, as seen in osteolysis or weight lifter's shoulder.

Glenohumeral osteoarthritis often presents with a slow, progressive onset of pain over an extended period of time, with less intense night pain than with rotator cuff disorders, but possibly a more substantial loss of motion, especially external rotation and overhead elevation. On examination, it is not uncommon to observe other joint involvement such as Heberden's nodes or hip and knee symptoms. Active range of motion displays audible or palpable crepitus, which is the unmistakable sound of "bone on bone." Rotational AP views, scapular lateral, and axillary radiographs typically reveal a loss of joint space, marginal osteophytes, and subchondral sclerosis. Unless there is some question regarding the quantity and quality of glenoid bone stock, rotator cuff integrity, or infection, it is rare to require further imaging to devise a treatment plan.

Acute trauma to the shoulder resulting in fracture presents with the typical scenario of pain, swelling, ecchymosis, and possibly deformity. It does not pose a major diagnostic dilemma, but it is of utmost importance not to overlook associated osseous, soft tissue, and neurovascular injuries. In this situation, accurate fracture classification is entirely dependent on adequate plain radiographs. The most widely accepted classification of proximal humeral fractures is based on displacement of the anatomic and surgical neck and greater and lesser tuberosity fragments.[4] To treat these injuries, all four fragments must be identified radiographically. Most of these injuries can be diagnosed with plain radiographs consisting of at least a trauma series. Additional oblique radiographs can be helpful, but the addition of computed tomographic (CT) scanning to further delineate fracture fragments has not been found to appreciably change the diagnosis made on plain films. About 80% to 85% of proximal humerus fractures are minimally displaced and can be treated without surgery. Some two-part fractures are amenable to closed reduction, but the more unstable and comminuted injuries will require techniques ranging from open reduction and internal fixation to proximal humerus replacement.[5]

In conclusion, most shoulder disorders, be they chronic pain, instability, arthritis, or the result of acute trauma, can be diagnosed by a thorough history, physical examination, and plain radiographs without further advanced imaging techniques. Clearly, MRI, ultrasonography, CT arthrography, and other investigative aids have an important role in more clearly delineating the disorder in routine and not so routine cases, and their use should not be abandoned. Their judicious use is probably more beneficial to the system as a whole, including the patient. The fine art of the history and physical is still worth its weight in gold.

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Cure, Conservation, Confusion, Chaos

Her agony came from the fact that mastectomy would be curative, and it was hard to turn that down. A lesser procedure, while preserving her breast and her femininity, offered her somewhat less chance for a complete cure—but exactly how much less was unknown. Perhaps only a small amount less. It didn't seem worth losing her breast for a few percentage points.

Yet, maybe it was. It was the most difficult decision of her life. But medicine had failed her. The data upon which to base her judgment was weak, and we had shifted the burden of that judgment to her.[1]

THE ABOVE PARAGRAPH was written in 1991 about a woman with ductal carcinoma in situ (DCIS) of the breast and her difficult journey through the medical system as she searched for the "right" treatment. There were a number of "right" treatments then for her particular form of carcinoma, but each was flawed in some way, confounding her thoughts, making her decision more difficult. But that was 1991; it is now 1995, and we know more about DCIS. But is the decision-making process any easier?

During my five-year surgical residency in Boston in the 1960s, I never saw a case of DCIS, and I have no recollection of ever hearing of it during my training. If a patient with this type of cancer had presented at that time, she would have been treated with a mastectomy just like any other patient with breast cancer. During the 1960s, to most physicians, breast cancer was breast cancer. It was all the same, unless you were a specialist in diseases of the breast—and there were few of those.

The most prominent textbook of the time devoted solely to breast disease was written by Haagensen.[2] He defined intraductal breast cancer as a lesion that appeared to grow predominantly within the mammary ducts. That meant that a substantial proportion of the lesion, as much as 49%, could be invasive. Haagensen treated the lesion, like any other invasive cancer, with radical mastectomy. He reported that the average lesion measured 47 mm and that 62% of his patients with intraductal carcinoma had metastases to axillary lymph nodes.[2]

During the past 30 years, there have been tremendous changes in the diagnosis, treatment, and our understanding of breast cancer biology. Ductal carcinoma in situ is now defined as being wholly intraductal without any invasion. Instead of a clinical rarity presenting as a mass or nipple discharge, DCIS is now common, generally non-

TABLE 1.—*Van Nuys Prognostic Index (VNPI) Scoring System**

Score	Points 1	2	3
Size, mm	≤15	16-40	≥41
Margins, mm	≥10	1-9	<1
Pathologic classification	Non-high grade, without necrosis	Non-high grade, with necrosis	High grade, with or without necrosis

*Scoring: 1-3 points are awarded for each of the 3 different predictors of local breast recurrence. Scores of each predictor are totaled to yield a VNPI score ranging from 3-9.

palpable, and usually presents as a mammographic abnormality. Instead of one simple treatment, there are now several alternatives accompanied by a great deal of confusion. Instead of physicians deciding what to do and when to do it, as they did 30 years ago, patients now play a key role in the decision-making process.

So how is DCIS treated? Thirty years ago, the answer was simple. Today, it is much more complicated, requiring a thorough integration of the mammographic and pathologic findings. We now appreciate that DCIS is a heterogeneous group of lesions rather than a single disease; no single treatment is going to be appropriate for all lesions.

The long-awaited results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B17 were published in 1993.[3] This prospective, randomized study was supposed to solve, once and for all, the complex treatment controversy. More than 800 patients with DCIS excised with clear surgical margins were randomly assigned to two groups: excision only and excision plus radiation therapy. At five years, there was a statistically significant decrease in local recurrence of both DCIS and invasive breast cancer in patients treated with radiation therapy. These data led the NSABP to recommend post-excision radiation therapy for all patients with intraductal carcinoma who chose to save their breasts, a recommendation that may be too broad. The study was criticized for a number of reasons,[4,5] the most important being a lack of pathologic subset analysis.

Consider the following two patients, both of whom merit radiation therapy according to NSABP recommendations. Patient 1 is a woman with a 5-mm low-grade micropapillary DCIS widely excised with a minimum of 10-mm margins in all directions. Compare her with patient 2, a woman with a 20-mm high-grade comedo lesion with DCIS approaching to within 0.1 mm of the inked margin but not involving it. According to the NSABP, both of these patients should be treated with radiation therapy. At our facility, the first patient would receive no additional therapy. She would be carefully observed with physical examination and mammography every six months. The second patient would undergo a wide reexcision before a final treatment decision was made. Substantial residual disease approaching the new margins would earn a recommendation for mastectomy and immediate reconstruction; widely clear new margins with little or no residual cancer would earn a recommendation for radiation therapy.

The point is that the decision-making process regarding the treatment of DCIS is not much clearer now than it was in 1991. The article on DCIS by Barth and associates elsewhere in this issue of the journal presents a concise overview of the state of the art.[6] The references are excellent, as are the authors' interpretation of the current data. But if physicians want the definitive answer or a recommendation about how to treat a specific patient with DCIS, it will not be found in this overview. The authors offer no personal opinions. For physicians who do not know much about DCIS or who want to refresh what they already know, this overview is a perfect start. But if after reading it they want to know more, they are going to have to do more work.

I would like to share briefly the direction that our group has taken in its DCIS research. Although we have great respect for the NSABP and what they have accomplished, we have difficulty accepting the blanket recommendation for radiation therapy for all patients with DCIS who elect breast conservation.

There are numerous clinical, pathologic, and laboratory factors that might aid clinicians and patients wrestling with the difficult decisions regarding treatment. Our research has shown that nuclear grade, the presence of comedo-type necrosis, tumor size, and margin status are all important factors in predicting local recurrence in patients with DCIS.[7,8] By using a combination of these factors, it may be possible to select subgroups of patients who do not require irradiation, if breast conservation is elected, or to select patients whose recurrence rate is potentially so high, even with breast irradiation, that mastectomy is preferable.

We used the first two of these prognostic factors (nuclear grade and necrosis) to develop a new DCIS pathologic classification.[9] But nuclear grade and comedo-type necrosis are inadequate as the sole guidelines in the treatment selection process. Tumor size and margin status are also important. By combining all of these factors, we have developed the Van Nuys Prognostic Index (VNPI) (M.J.S., D. N. Poller, P. H. Craig, et al, "A Prognostic Index for Breast Ductal Carcinoma In Situ," unpublished data, 1995).[10] Table 1 shows the VNPI scoring system. Scores from 1 to 3 are awarded for each of the three different predictors of local breast recurrence—size, margins, and pathologic classification. The scores for each predictor are totaled to yield a VNPI score ranging from a low of 3 to a high of 9. Patients with a low VNPI score (3 or 4) show no difference in disease-free survival at eight years regardless of whether or not they received radiation therapy and can be treated with excision only. Patients with intermediate scores (5, 6, or 7) show a statistically significant decrease in local recurrence rates with radiation therapy. Conservatively treated patients with VNPI scores of 8 or 9 have unacceptably high local recurrence rates, regardless of irradiation, and should be considered for mastectomy.

We first introduced the idea of a prognostic index for DCIS at the 1995 Annual Meeting of the Society of Clinical Oncology. Since that time, we have analyzed an outside group of patients with DCIS, confirming the validity of the VNPI. We plan to present this combined analysis of 540 patients with DCIS at the 18th Annual San Antonio (Texas) Breast Symposium in December 1995.

The VNPI is the first attempt to quantify known important prognostic factors in DCIS, making them clinically useful in the treatment decision-making process. In the future, other factors, such as molecular markers, may be integrated into the VNPI when they are shown to statistically influence the likelihood of local recurrence after breast conservation therapy.

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Coronary Artery Involvement in Kawasaki Disease—Diagnosis and Treatment

To the Editor: The article in the April 1995 issue by Joffe and colleagues regarding complicated Kawasaki disease and the importance of early diagnosis and treatment made interesting and informative reading.[1] As they say, infants may have an atypical clinical course, resulting in delayed diagnosis and initiation of treatment, which is of paramount importance as regards the disease's often fatal coronary artery involvement. In this context, we would like to draw attention to some additional data relevant to the subject.

The use of two-dimensional echocardiography for the early detection of coronary aneurysm and the simple dilatation and thrombosis of coronary arteries in Kawasaki disease is imperative. In a retrospective study of 44 patients with Kawasaki disease examined during the first two weeks of illness and observed for as long as six months, Ichida and co-workers analyzed the correlation between electrocardiographic (ECG) changes and echocardiographic abnormalities.[2] Of the 44 patients, 34 (77%) had ECG abnormalities, 68% appearing during the first week, 50% in the second to third week, 16% at two months, and 10% at three months. The chances of having an abnormal echocardiogram increased with the number of ECG changes: a risk of 0% for no change, 37% with one change, 47% for two, 80% for three, and 100% for four changes in serial ECGs. Whereas ECGs showed abnormalities in 77% of the cases, echocardiography showed changes in 41%. Hence, the monitoring of serial ECGs may play a role in complementing the use of echocardiography in the detection of coronary artery lesions in acute Kawasaki disease.

Although the authors recommend the use of echocardiography for prolonged illnesses with thrombocytosis in infants, Kinney and associates describe the case of a patient with atypical Kawasaki disease having coronary aneurysms with thrombocytopenia. They suggest that echocardiography should be considered in febrile infants with thrombocytopenia of uncertain cause.[3]

The detection of predictive markers for coronary artery complications in patients with Kawasaki disease is gaining importance. Ogawa and co-workers compared the variation in plasma endothelin-1 levels by the sandwich-enzyme radioimmunoassay method during each of the clinical stages of Kawasaki disease in 30 patients (ages 4 to 62 months).[4] They found this measurement to have a 100% sensitivity and 96% specificity as a predictor of coronary artery dilatation in the acute stage of Kawasaki disease (5.13 ± 1.64 pg per ml for the positive group versus 3.09 ± 0.70 pg per ml for the negative group; $P < .01$). Other markers used for predicting coronary artery involvement are increased urinary neopterin concentrations,[5] decreased expression of CD23 on peripheral blood macrophages or monocytes,[6] and increased intracellular adhesion molecule-1 levels in the serum.[7]

Finally, although the use of intravenous γ-globulin (IVGG) therapy with salicylates has been of immense help in reducing the incidence of coronary artery complications, Furukawa and colleagues compared the efficacy of administering oral pentoxifylline and IVGG in combination with that of IVGG alone in reducing the frequency of coronary artery lesions in patients with Kawasaki disease.[8] Oral pentoxifylline was given as 10 mg per kg per day (low dose) and 20 mg per kg per day (high dose) in three divided doses up to the 30th day, along with 200 mg per kg per day of IVGG for 5 consecutive days. With the use of two-dimensional echocardiography twice a week, they detected coronary artery lesions in 3 of 21 patients (14%) in the IVGG therapy groups versus 0 of 22 patients (0%) in the high-dose pentoxifylline and IVGG combination therapy group ($\chi^2 = 6.4$, $P < .02$).

The above data, in conjunction with those presented by the authors, help us better understand and diagnose this important complication of Kawasaki disease.

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More on the Use of Ultrasonography in the Emergency Department

To the Editor: The comments by Steven J. Sainsbury, MD, in the June 1995 issue[1] sound familiar to those of us in family medicine who have recognized and published the benefits of ultrasonography-assisted diagnosis in family medicine.[2-4] Some of this has been described in the emergency medicine literature.[5]

In our Department of Family Medicine with a section of emergency medicine, our physicians are required to

provide first-hour care in many rural and underserved communities. In particular, we have incorporated diagnostic ultrasonography into our daily practice of obstetrics-capable family practice and emergency medicine. Our family practice training programs are required to teach the residents and faculty these diagnostic ultrasonographic skills.

In our hands, the most frequent use for ultrasonography is in the diagnosis of pregnancy-related problems. For example, during the investigation of a possible ectopic pregnancy, our most frequent result is the documenting of a healthy intrauterine pregnancy. This allows for appropriate reassurance, discharge from the office or hospital, and follow-up. Among our patients, quality of care has been improved, costs have gone down, and patients are happy with the transfer of this technology into primary care. As others have said, the ultrasound machine will probably be the stethoscope of the 21st century.

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To the Editor: In response to the letter of Steven J. Sainsbury, MD,[1] regarding the use of ultrasonography by emergency physicians, several issues need to be addressed.

Currently most emergency physicians lack the expertise and training in the full range of ultrasound examinations and procedures and, in many instances, fail to meet the minimum criteria of the American Institute of Ultrasound in Medicine. This body requires, as a minimum, 500 diagnostic ultrasound examinations done and supervised in residency or, lacking that, evaluation, interpretation, and supervision by a qualified physician of 500 sonographic cases within a three-year period in a postdoctoral experience. Radiologists in all of their four years of residency training are specifically trained in sonographic imaging and have both written and oral examinations for board certification covering not only the diagnostic criteria, but the physics and instrumentation involved in sonography.

Most radiology practices have a full range of ultrasound equipment, including portable units that can be taken to the emergency department and trained technicians to meet the needs of the practice, which would need duplication if emergency physicians would also require the technology to fill only one niche of practice. Radiologists also have the means to dictate the reports, store the images for retrieval, and mechanisms in place to monitor and calibrate the equipment for optimal functioning. In addition, they are well versed in correlating the sonographic diagnoses against other diagnostic imaging studies.

On the other hand, radiologists need to be ready to fill the needs of emergency physicians in a timely manner and able to offer their services nights and weekends. In point of fact, most sonographic studies generated from the emergency department are not immediately life-threatening, such as pericardial tamponade, symptomatic aortic aneurysm, ectopic pregnancy with cardiovascular instability, and abdominal trauma. Most sonographic studies fall into a category of urgent but not immediately life-threatening, such as acute cholelithiasis or deep venous thrombosis.

Of concern to all those who do use ultrasound equipment is that if those who do it are not well trained to the nuances that exist and miss substantial disease, the imaging method loses credibility. For instance, it is not uncommon for the uninitiated examining the aorta for aneurysm to miss such things as retroperitoneal adenopathy, horseshoe kidney, and retroperitoneal fibrosis, all important considerations that may affect a patient's prognosis. Such misses also involve professional liability. Whereas an emergency physician may only wish to do a limited study, many incidental findings are the rule, and less-trained practitioners will not recognize them. A course or two on ultrasonography is no substitute for a rigorous training program with supervision by well-trained ultrasonographers.

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Dr Sainsbury Responds

To the Editor: Dr Gooding is correct in pointing out that primary care providers, such as emergency physicians, who perform limited emergency ultrasonographic studies will consistently lack the expertise and experience of radiologists. To do a complete and comprehensive ultrasound examination is not the goal of emergency physicians. Our goal is to quickly recognize life-threatening conditions such as ectopic pregnancy, abdominal aneurysms, or pericardial tamponade. After

the emergency, complete and comprehensive follow-up ultrasound studies can be appropriately done by radiology department personnel.

Radiologists perform admirably in comprehensive ultrasonography. Likewise, cardiologists, obstetricians, and trauma surgeons effectively use limited ultrasonography for specific purposes. Joining this group are emergency and other primary care physicians who can effectively use this valuable technology in a specific, limited, and immediate manner.

Courses in emergency ultrasonography are not intended to substitute for a radiology residency. They do, however, provide emergency or primary care physicians valuable information about a patient that on-call ultrasonography cannot. If ultrasonography is to be the stethoscope of the 21st century, we must allow equity in its use.

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Silicone Implants in Men

To the Editor: Teuber and colleagues in the May 1995 issue of The Western Journal of Medicine[1] address a problem that has been extensively studied and reported in the medical press, the national lay press, and other media. The extensive silicone gel implantation in men, however, which also began in the early 1960s, has all but been ignored. There exist as many as 400,000 testicular silicone implants, with initial implantations done more than 30 years ago. Would it not behoove the investigators to include men in their future investigations of silicone and their outcome-oriented studies?

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Congenital Malaria in Twins

To the Editor: Balatbat and colleagues, in their interesting report (in the May issue of the journal) of malaria in a young twin,[1] suggest that congenital malaria may remain "relatively rare" because of underreporting. Certainly, it is difficult to diagnose, and thus report, "classic" congenital malaria in endemic areas. As described by the authors, a classic presentation of congenital malaria includes fever, anemia, and splenomegaly during the second month of life. For children with such presentations in malaria-endemic areas of the world, it would not be possible to differentiate cases of congenital malaria from those acquired from mosquitoes. The diagnosis and reporting of such cases are thus limited to areas of the world where malaria does not usually occur.

The authors refer to the "rarity of congenital transmission" of malaria.[1] Actual transplacental transmission of *Plasmodium* is not uncommon, however. Reports show that as many as 29% of newborns in tropical Africa may be born with malaria.[2] Many of these children remain asymptomatic, but neonatal malarial infection has been associated with fever and death.[3]

Indeed, the question of malaria in newborn twins has not been well studied. This report prompted us to review recent data from an ongoing study of congenital malaria in Zaire. There were five pairs of twins among 337 births. Each mother of twins took prophylactic chloroquine and was smear-negative at delivery. Overall, 14 (4.2%) newborns had cord blood smears positive for malaria. One (10%) of the twins, the first twin born to a woman in whom fever developed and who had a positive malaria smear on the second postpartum day, had a positive smear. Multiple gestation was not significantly associated with the presence or absence of congenital malaria ($\chi^2 = .88$; $P = .35$). Pending larger studies, these initial data confirm that the congenital transmission of malaria to twins may be discordant and suggest that the frequency of prenatal transmission of malaria to twins is not substantially different from that to singletons.

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Drs Balatbat, Jordan, and Halsted Respond

To the Editor: We are grateful that Drs Fischer, Nyirjesy, and Toko have shared their larger experience on congenital malaria. Certainly in malaria-endemic areas of the world, it would be much more difficult to differentiate congenital malaria from mosquito transmission following delivery. Mosquito transmission of malaria in California has been documented occasionally. This was not known to have occurred in the Yuba City area at the time that our patient was seen. A large group of immigrants from Punjab, India, inhabit a farm community in the Yuba City area. With the travel of these persons and their families to and from India and the occasional relapse of malaria after long periods, this disease is not infrequently seen at the Sacramento Medical Center in both adults and children.

It is of interest that the congenital transmission of malaria to twins is discordant, as was the case with our patient. Data on malaria transmission to monozygotic twins are even more limited.

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Sarcoidosis and Beryllium Exposure

To the Editor: In the June 1995 issue of the journal, both Chesnutt[1] and Sharma[2] allude to the elusive nature of sarcoid disease and its diagnosis—the search for an etiologic agent, the factors instigating fibrosis, and recognizing the system-specific changes reflected in the presentation of a patient with sarcoidosis. I was surprised to find that neither diagnostician commented even briefly on the need to exclude beryllium exposure (occupational or environmental) in a patient's differential diagnosis. In Harrison's classic *Principles of Internal Medicine*, the need for a detailed clinical history is summed up as follows[3(p1071)]:

> Histologically, it may be difficult to differentiate the chronic form of [beryllium] disease from sarcoidosis. Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, high technology ceramics, and before the 1950s in the production of fluorescent lights, one may miss entirely the etiologic relationship to an occupational exposure.

The need for an occupational history before characterizing "nonspecific lesions" as sarcoidosis has been further amplified.[4] The pulmonary presentation of nonspecific lesions—epithelioid granulomas with or without minimal necrosis or cytoplasmic inclusions—are characteristic of many other conditions besides sarcoidosis.[5]

My sole purpose for this correspondence is to remind those in primary care and internal medicine specialties about the fact that patients spend between a third and half of their working lifetime in a possibly complex-chemical job environment. The need to inquire, What do you do in your job, and what materials do you handle? cannot be ignored in establishing a differential diagnosis for sarcoid disease.

Once a history reveals a potential for unique or exotic exposures, clinicians should take the time to check their own library sources, ask the local university biomedical library to run a search, or seek counsel from an occupational medicine associate. If the medical evaluator fails to ask the questions that go beyond, "What is your occupation?" the potential may never be realized, and another elusive diagnosis may be lost.

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* * *

Dr Chesnutt Responds

To the Editor: I appreciate Dr Cohen's emphasis of the importance of a thorough occupational history in the diagnostic evaluation of granulomatous lung disease. As I mentioned in my article, "a careful history and physical examination, including an occupational history," is crucial in the diagnostic evaluation of a patient with suspected sarcoidosis. Such an evaluation is important because the clinical features of berylliosis are similar to those of sarcoidosis and include dyspnea, cough, weight loss, and fatigue. Chest radiographs of patients with chronic beryllium lung disease also usually show nodular or irregular opacities; hilar adenopathy is seen in 40% of cases.

In addition, as Dr Cohen astutely points out, chronic beryllium lung disease is histologically identical to sarcoidosis. In contrast to sarcoidosis, however, additional analysis of bronchoalveolar lavage fluid and lung tissue specimens can be done in patients with suspected berylliosis to help clarify the diagnosis. Proliferative responses of lung T cells to beryllium and chemical analysis of lung tissue for beryllium may yield useful information in patients with berylliosis. Once the diagnosis of beryllium lung disease is documented, however, therapeutic options are as limited as they are in sarcoidosis; corticosteroids are currently the mainstay of therapy for both disorders.[1] In addition, patients with beryllium lung disease should be counseled to ensure that they are no longer exposed to beryllium.

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Lessons From the Practice

The Trouble With Functional Illness

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We call an illness functional when the physical examination and test results are all within normal limits. What troubles me is the possibility that if I look hard enough and smart enough, I will always find that elusive positive finding. At what point should I stop testing?

My patient, Irene, is a tough-looking woman of 67. She is always accompanied by her husband, who is the strong, silent type. When he speaks, it is to confirm what his wife says. She speaks with power and sometimes with thunder.

"I'm tired. Everything hurts. I can't do the housework. I can't even cook. And my husband doesn't lift a finger! Now that he is retired, he does not want to do anything for himself. It is too much. I can't do it anymore."

"That's right, Doctor, she is not herself. She can't do anything. She hurts all the time," her husband adds.

"Where does it hurt?" I dutifully ask.

"Here in my shoulders, and here in my back and here in my hips and my legs and here in my neck. And my knees sometimes." As she speaks, she jabs herself with her powerful finger at each anatomic site.

The examination results are negative as are the blood tests, and the x-ray films are normal. My approach is to recommend ibuprofen and exercise and to talk with the husband about helping his wife more around the house. He promises to try, even though he insists that he already does everything she asks.

Weeks go by, and nothing helps. With each visit, she is more demanding and more angry. She describes fatigue and weakness, but her voice is strident and overpowering. She is so angry that I am afraid to suggest that her problem may be anger.

I am at a loss, and there are no objective signs. Moreover, her illness appears to "function" as a means of expressing her anger. I am ready to make a judgment: Irene has a functional illness. But I must ask the rheumatologist whether more tests might uncover an objective basis for her symptoms.

"I don't know what to make of her symptoms, either," he says. "Just as you said, the tests are negative: normal sedimentation rate and negative autoimmune antibodies. Her temporal artery is not tender, and there is not enough to suggest chronic fatigue syndrome. But she wants to see me again, so I will observe her for a while. By the way, she is really angry at her husband."

I call a psychiatrist friend and describe the situation. He asks, "Well, what do you think needs to happen?"

"Someone ought to talk to them and give her a safe place to express her feelings more directly to her husband. What she is doing now is holding her anger in and displacing it into her body."

My friend agrees to see the patient and her husband. At last, I am ready to confront Irene. I rehearse my lines in case I become the next target for her anger. She preempts me, though, by appearing completely cured.

"You look great! What happened?" I blurt. Indeed, she looks 20 years younger, and for the first time she is smiling. Her husband also has a satisfied expression on his face.

In a calm, almost serene voice she says, "I am on prednisone now. The rheumatologist said my sed rate went up on the last visit, so he started me on steroids. I am fine. I have PMR."

Her illness is polymyalgia rheumatica. Months later, she continues to do well on low doses of prednisone, and she has stopped complaining about her husband.

I had been positive that Irene was a perfect example of a psychosomatic or symbolic illness. The sudden jump in the sedimentation rate changed the diagnosis. Yet, I have little doubt that illnesses often do contain messages and meanings relevant to our psychosocial and spiritual existence. All suffering is an opportunity for growth and understanding. An illness may be the vehicle in which we arrive at a wholeness of the soul.

In this era of managed care, I don't want to repeat negative tests or to do unnecessary ones. But when should we stop looking for the clue that will show that the symptoms are not the result of the anger, but that the anger is the result of the symptoms?

(Orvell B: The trouble with functional illness. West J Med 1995; 163:397)

Dr Orvell is in private practice in Vacaville, California.
Reprint requests to Barry Orvell, MD, 3000 Alamo Dr, Ste 102, Vacaville, CA 95687.

Lessons From the Practice

An Act of Faith

DANA F. HOCH, MD, *San Jose, California*

John's appearance startled me; he grinned contentedly and radiated warmth and good health. I had known him for more than three years, and for most of that time his eyes carried that heavy-lidded gloom seen in the faces of the chronically ill. Now they sparkled. We sat together in the examination room, his first visit in three months. For a month or so I had been wondering why I had not seen him in the emergency department.

John was 55, a Mexican American from the *barrios* of Los Angeles. During most of the 1960s and 1970s, he had been alternately a heroin addict and a convict. He eventually "kicked the habit," but turned to alcohol, which led to the development of cirrhosis and esophageal varices. He managed to stop drinking and received a portacaval shunt; about that time he started coming to the clinic. As if he were being paid back for earlier sins, John developed diabetes mellitus and asthma. He was predictably in the hospital every other month or so, for one reason or another. I saw him in clinic monthly and thought I knew him well.

"I know you will think I am crazy," he said, "but three months ago I tossed all my medication into the garbage. I decided they weren't doing me any good. And now I feel great, not like before."

John sounded confident, hardly the self-pitying, angry man I had seen so frequently. He sat there, all stylish in pressed navy blue slacks, grey sports shirt open at the collar and tasseled, well-shined loafers. Despite his medical problems, he still had the build of an athlete. His biceps swelled to the size of cantaloupes as he gestured and rippled the tattoos he wore up and down his arms.

"Yeah, my ammonia and my sugar levels used to go off the wall if I ate even a little peanut butter. Now I can have a peanut butter and jelly sandwich, go over to the church and work, and still feel okay."

"Oh, is that right?" I answered skeptically. I began writing in his chart, perplexed and a little upset by the fact that without my help, without medications, he was in better shape than I had ever seen him. It made no sense.

Suddenly he turned to me. "Doc, are you a Christian?"

His question and the unblinking, piercing gaze embarrassed me. "Well, yes . . . I guess so," I said uneasily, trying to conceal my discomfort. John had touched a sensitive nerve.

"My father is a Lutheran pastor, and I was raised in the church," I admitted, "but I don't think I ever really believed much of it; over the years I just sort of lost interest." I sighed a moment, a palpable silence between us.

John continued. "About four years ago, when I stopped drinking, my wife and I joined a Hispanic Christian church. I never went much, but they kept me clean and off the booze. Then the last time I was in the hospital, when I was so sick, it came to me that Jesus can perform miracles. I knew if I gave myself up to Him, I didn't need all those pills. You probably don't believe me, but it's true."

John had never spoken to me of religion. I had not asked him about anything other than his medical conditions. His intimidating tattoos and past history bespoke nothing of the kind of Christians I knew or the Holy Trinity I had learned about as a child.

I directed him to the examination table. "I sure do believe what you told me. I'm just happy you feel well and are active in your church." The examination was normal and his finger-stick glucose level better than it had been in many months. On the way out of the room, he turned and said, "I listen to religious tapes. They give me strength to keep going. None of us is alone, Doc."

We shook hands, his meaty, firm grip enveloping mine. "I'll see you if you think I can help," I said. "But whatever you are doing, keep it up. Good luck, John." Those were the last words we ever exchanged.

Three months later, John died. The paramedics brought him to the hospital nearly dead, and he survived a couple of days. His wife told me of the solace John had found during the final six months of his life. The demons he had carried around were cast out. In their place were tranquility and a sense that because of his faith in the Christian symbols, his life had meaning. Spiritually and, for a time, physically, he had been restored.

John taught me that a healing, life-affirming presence exists in every person. Discovering how to tap its power does not come easily; for some, this happens only after years of self-destructive behavior and suffering.

We all have our personal demons; I know mine all too well. Perhaps I will not follow an organized church or creed, but I understand, deep in my gut, that those demons will not go away by themselves.

(Hoch DF: An act of faith. West J Med 1995; 163:398)

From the Primary Care Department of Medicine, Santa Clara Valley Medical Center, San Jose, California.
Reprint requests to Dana F. Hoch, MD, Chaboya Clinic, 2410 Senter Rd, San Jose, CA 95111.

Poem

Lichenplanus

for Gilly

I wear a scarf to cover my crown
it's cold with no hair

first one lock
then another

tufts of my wavy
blonde pride tangle on the pillow

I am coming undone
a sweater unravelling

sea grass on a sand dune
Sinead O'Connor

old and wrinkled
without the voice

my husband takes me to the teaching hospital
the students show up early

naked as a knee my shiny skull
a door knob sandblasted by solar winds

biopsies, close ups, videos, probes
no prognosis, the specialist is vague

"more cortisone," "immunosuppressants"
Cure there is none

hair could grow where skin's unscarred
Unlikely

even bald as a coot
he says he loves me

back to the sand dune
Lichenplanus

stone bald at 50,
smooth as an egg now

not a whisper of fuzz
just untouched skin

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Tiburon, California

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- Alerts, Notices, and Case Reports: 1,500 words
- Lessons From the Practice: 1,000 words
- Letter to the Editor: 500 words

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(Continued from Page 332)

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

January 29-February 2—**Occupational & Environmental Medicine I.** UCSF at Miyako Hotel San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF

ONCOLOGY

December 3—**Tumor & Tumor-Like Conditions of the Bone**. California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sun. 8 hrs. Contact: Anne E. Chism CTTR, c/o Loma Linda University, School of Medicine, Dept. of Pathology, 11021 Campus Ave. , AH 335, Loma Linda 92350. (909) 824-4788.

OPHTHALMOLOGY

November 18—**Diabetes and the Eye**. MMI/UCI Center for Health Education at Long Beach Memorial Medical Center. Sat. Contact: Center for Health Education, (310) 933-3811.

January 27—**Genetic Disease & the Eye.** Cedars-Sinai Medical Center at Hotel Sofitel, Los Angeles. Sat. 7 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Room 2211, Los Angeles 90048. (310) 855-2937.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists.** Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, P O Box 1216, Murrieta, CA 92564. (909) 677-4482.

ORTHOPEDICS

November 9-11—**Integrated Function of the Lumbar Spine and Sacroiliac Joints.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 15 hrs. $335. Contact: UCSD.

November 30-December 1—**Disorders of the Upper Extremities.** UCSF at Miyako Hotel, San Francisco. Thurs-Fri. 12 hrs. $375. Contact: UCSF.

OTOLARYNGOLOGY

November 12-17, December 9-15—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 2-4—**San Francisco Otology-Neurotology—1995**. UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 22 hrs. $425. Contact: UCSF.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists**. Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, P O Box 1216, Murrieta, CA 92564. (909) 677-4482.

PATHOLOGY

November 3-5—**45th Annual Meeting of the National Kidney Foundation**. California Convention Center, San Diego. Fri-Sun. 17 hrs. Contact: NKF, 30 E 33rd St, New York, NY 10016. (800) 622-9010.

November 10-11—**Pathophysiology and Treatment of Gastroesophageal Reflux**. USC at at Health Sciences Campus. Fri-Sat. 16 hrs. Contact: USC.

PEDIATRICS

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 19-21—**Practical Pediatric Electrophysiology and Pacing Course.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. Contact: Children's Hospital and Health Center, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 22-26—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital and Health Center at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. Contact: Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 26-28—**34th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15hrs. $295. Contact: David Steward, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 1-3—**Current Concepts in Pediatric Medicine**. Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego, CA 92123. (619) 576-4072.

PLASTIC SURGERY

November 4-5—**Endoscopic Plastic Surgery and Beyond**. UCSD. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

November 11-14—**Surgical Advances in Cleft and Cleft Palate.** UCD at Monterey Plaza. Sat-Tues. 18 hrs. $450. Contact: UCD.

December 8-9—**2nd Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources. Fri-Sat. Contact: Martin Borsanyi, c/o Professional Image, (714) 760-1522.

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face**. UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

November 3-5—**41st Annual Group Therapy Symposium**. UCSF. Fri-Sun. Contact: UCSF.

February 11-13—**29th Annual Recent Advances in Neurology**. UCSF at Ritz-Carlton, San Francisco. Sun-Tues. Contact: UCSF

February 12-17—**AGPA National Conference and Institute: Toward Total Health: Groups to Heal the Mind and Body.** Northern California Group Psychotherapy Society at San Francisco. Mon-Sat. Contact: Ann Steiner, Ph.D., NCPGS, 821 East Second St., Ste. 203, Benicia 94510. (415) 442-1976.

PULMONARY/CRITICAL CARE

December 1-2—**Laser Bronchoscopy, Stents, Brachytherapy, Thoracoscopy for the Pulmonologist and Emphysema Surgery.** MMC/UCI Center for Health Education at Long Beach Memorial Medical Center. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

RADIOLOGY

November 2-4—**8th Annual Obstetrical and Transvaginal Ultrasound Course—A Hands-On Course**. MMC/UCI Center for Health Education at Doubletree Hotel, Orange. Thurs-Sat. Contact: Center for Health Education, (310) 933-3811.

January 28-29—**Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel Del Coronado San Diego. Sun-Mon. 16 hrs. $375. Contact: UCSD.

January 28-February 4—**Multispecialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest Ultrasound and Bone.** UCSD at Hotel del Coronado, San Diego. 1 wk. 40 hrs. Contact: UCSD.

March 10-15—**Neuro and Musculoskeletal MR**. UCSD at Hotel del Coronado, San Diego. Sun- Fri. 28 hrs. $425-$625. Contact: UCSD.

SURGERY

December 1-3—**International Symposium on TMJ Arthroscopy and Arthroscopic Surgery**. Fri-Sun. $695. Contact: Peg Hoelderlin, c/o Professional Image, (714) 760-1522.

January 5-9—**19th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Pan Pacific Hotel, San Diego. Tues-Fri. 26 hrs. $475. Contact: UCSD.

January 12-13—**What's New In General Surgery: 18th Annual Postgraduate Course.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $285. Contact: UCD.

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

December 23-29—**Advances in Medicine 1995**. Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Fri. 6 hrs. $475. Contact: Symposium Maui, PO Box 10185, Lahaina, HI 96761. (808) 661-8032.

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January 17-20—**Medicine Meets Virtual Reality 4: Health Care in the Information Age—Future Tools for Transforming Medicine**. UCSD at San Diego Convention Center. Wed-Sat. 23 hrs. $450. Contact: UCSD.

February 19-23—**Physician Heal Thyself**. UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 20-21*—**ECG, Interpretation for the Primary Care Physician**. New Mexico Heart Institute at the Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, NM Heart Institute, 1001 Coal SE, Albuquerque 87106. (505) 841-1001 or (800) 888-6642.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic Scottsdale, 13400 E Shea Blvd, Scottsdale 85259. Phone, (602) 301-7447; fax (602) 301-8323.

December 7-9—**American College of Physicians, New Mexico Chapter, and New Mexico Society of Internal Medicine—Scientific Session**. Hilton Inn, Albuquerque. Contact: Carol Case, UNM SOM.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Fri-Sat.. Contact: Billie Dytzel, (505) 265-0732.

February 24-25—**Mammography: Practical Challenges of the 90s for the Technologist.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax, (404) 552-9859.

February 24-27—**Mammography: Practical Challenges of the '90s: Managed Care, MQSA, and the Radiologist's New Role as Care Giver**. X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax, (404) 552-9859.

*Corrected date

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

October 27-29—**Intensive Interactive Head and Neck Imaging Course**. University of Utah at Marriott Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Contact: UUMS.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

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Special Issue Editors, 1995

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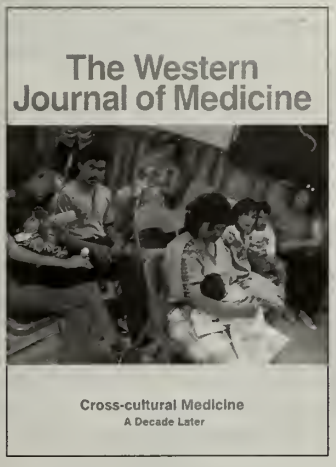

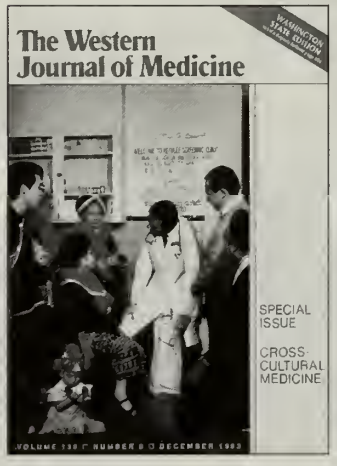

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(Continued from Page 402)

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 21—**Practical Pediatrics.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

October 21-22—**ACLS**. Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

October 25—**The Changing Workplace: Effective Measures to Cope With Job Stress.** Seattle. Wed. Contact: Center for Occupational Health and Safety, (206) 543-1069.

October 26-27—**Current Concepts in Drug Therapy**. Seattle. Thurs-Fri. Contact: U/W.

October 27—**7th Annual Current Concepts in Perinatology**. Tacoma. Fri. Contact: Multicare, (206) 552-1221.

October 27-28—**Mental Health Update: Training in...**Seattle. Fri-Sat. Contact: U/W.

November 2-3—**Ergonomics of Occupational Hand-Arm and Whole-Body Vibration.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 3—**Reproductive Endocrinology**. Seattle. Fri. Contact: VMMC.

November 8—**Pain Management.** Northwest Hospital, Seattle. 4 hrs. Contact: Educational Services, Northwest Hospital, (206) 368-1623.

November 10-11—**6th Annual Regional Conference for Occupational Therapy and Physical Therapy.** Seattle. Fri-Sat. Contact: U/W.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

Novembr 13—**New Ways of Organizing Data: Geographical Information Systems.** Seattle. Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

November 16-18—**Surgery Update**. Seattle. Thurs-Sat. Contact: U/W.

November 17—**Pinkham Basic Science Lectureship**. Seattle. Fri. Contact: Swedish, (206) 386-2265.

November 24—**Urology Update.** Seattle. Fri. Contact: VMMC.

November 30—**Air Pollution: Has Particulate Matter Increased Mortality? Lessons From Seattle and Spokane**. Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 1—**Pediatrics Update**. Seattle. Fri. Contact: VMMC.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9—**Fiberoptic Intubation**. Seattle. Sat. Contact: U/W.

December 14—**Clinical Recognition of Health Hazards in the Home.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety.

December 14-16—**Primary Care for the Ob/Gyn**. Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference**. Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

January 11-12—**Ergonomics**. Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 20—**Pharmacology Update**. Seattle. Sat. Contact: Swedish Hospital, (206) 386-2265.

January 25—**Ethical Issues in Occupational Health**. Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

THE WESTERN JOURNAL OF MEDICINE

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- **Contact** Aggie Hedin at James Russell, Inc, PO Box 427, Bloomington, IL 61702-0427, (800) 822-2566, x226 or FAX (309) 663-4470.

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
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Call (800) 873-0786; FAX (209) 252-3085

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NORTHWEST PERMANENTE, P.C., a physician-managed multispecialty group serving 380,000 members of Kaiser Permanente, has long-term locum tenens opportunities available for BC/BE Family Physician or Internist (full-time and part-time) in the Portland area.

Ours is a collegial and stimulating practice with a predictable schedule and the opportunity to experience the quality of life inherent to the Pacific Northwest. Competitive salary plus family medical coverage, paid leave time, professional liability coverage and assistance with moving expenses. Forward inquiry and CV to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah, Suite 100, Portland, Oregon 97232-2099. Call 800-813-3763. EOE.

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HAWAII — Clinic needs FP/Outpatient; FP/OB or OB/GYN with—w/out Terminations; Pediatrician — (Kona). Guar/Benes. **West Palm Bch FL** — FAMILY PRACTICE, OB/GYN; **OAHU** — MED DIR, $150K. In Honolulu: call (808) 947-9815. CVs:

LAM Associates, Dept W, 444 Hobron Ln, #207H, Honolulu, HI 96815-1229.
Call Pat Lam, 11am-11pm PST: 1-800-258-4526.

Health Center
MEDICAL DIRECTOR

$86,469-$105,131. SF Dept of Public Health seeks applicants for Medical Director of Health Center #4, a community-based full-service clinic, to provide supervision and oversight of primary care services plus direct patient care. Community served is largely monolingual Chinese. Requires: Board-certified or eligible physician in primary care specialty, 2+ years post-residency. Strong preference for bilingual in Cantonese, exp in community clinic in multicultural environment.

Send CV by November 16 to: Madeline Ritchie, Ctr Director, Health Ctr 4, 1490 Mason St, San Francisco, CA 94103.

DEADLINE

for the December Classifieds is Friday, November 3.

INTERNAL MEDICINE

Opportunities

If quality of life is important to you, call us now. Enjoy a relaxed lifestyle while practicing general internal medicine in Tucson, Arizona.

Thomas-Davis Medical Center, one of the nation's oldest and premier medical groups, is adding several BC/BE physicians to its staff.

Excellent salary and benefit packages. Call Dee Pones, (800) 658-9166. FAX CV (520) 322-2676.

THOMAS-DAVIS MEDICAL CENTERS

Tired of long commutes and polluted skies?

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Female OB-GYN and CNM seeking OB-GYN or FP for woman's clinic. OB-GYN practice needs practitioner(s) to take over. Costs and time-frame negotiable. If you want a safe and supportive environment for you and your family, this is the place!

Contact: (801) 750-0366, 0377 or 753-1547
Send CV to: 550 E 1400 N, Suite R, Logan, UT 84341

❑ **WESTERN WASHINGTON** ❑

Excellent opportunity for a BC/BE General Internist to associate with established Internist in a multispecialty clinic on the Kitsap Peninsula. Available August 1, 1995. Near boating, hiking, and fishing activities. Great place to raise a family and retire. Send CV to **James Gillick, MD, 20700 Bond Rd NE Poulsbo, WA 98370. Telephone (360) 779-9911**

INTERNAL MEDICINE

Northern California multispecialty group has immediate opening for practitioner. Clinical activities involve full range of Internal Medicine. Competitive salary and comprehensive benefit package. CV to: **10978 Donner Pass Rd, Truckee, CA 96161.**

Primary Care Practitioner

Planned Parenthood/San Mateo County. Part-time. BC/BE in Family Practice or Internal Medicine. Adept in dealing with ethnically diverse, predominantly female patients. Supervise NPs and PAs. Prefer previous managed care exp. **CV to: Ann Forrister, 2211 Palm Ave, San Mateo, CA 94403.**

NORTHERN CALIFORNIA—INTERNIST to replace retiring associate in active fee-for-service practice. One-in-five call. Enjoy excellent rural quality of life in beautiful Sierra Nevada Foothill community. Boundless recreational opportunities. Within one hour of metropolitan area. Contact: Internal Medicine, 815 Court Street, #7, Jackson, CA 95642, or call (209) 223-3837.

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 18 years. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (503) 482-4951.

FAMILY PRACTICE PHYSICIAN. BE/Residency trained family practice physician wanted for broad spectrum office and inpatient family practice in S. San Diego County. Salary guaranteed with incentives. Send CV to Primary & Specialty Physicians Medical Group, Inc, 480 Camino Del Rio South, Ste 121, San Diego, CA 92108. (619) 299-4770; FAX (619) 299-8153.

STAFF PHYSICIAN—PT or FT. The Sacramento Medical Foundation Blood Center is seeking a physician to assist with medical and clinical evaluation of blood donors and patients undergoing plasma exchange. IM/Path preferred. Malpractice Ins provided. Send CV with salary history to Janet Tulley, Dir of Human Resources, Sacramento Medical Foundation, 1625 Stockton Blvd, Sacramento, CA 95816, (916) 456-1500. EOE/AA.

INTERNAL MEDICINE-CRITICAL CARE PHYSICIAN. Highly respected, credentialed, experienced, and personable internist, preferably with critical care interests and training, for full-time inpatient only practice in San Diego County. Rotating call with similar credentialed physicians. No private practice or office activity involvement. Emergency medicine experience helpful. Salary guaranteed, plus incentives. Send CV to Primary & Specialty Physicians Medical Group, Inc, 480 Camino Del Rio South, Ste 121, San Diego, CA 92108. (619) 299-4770; FAX (619) 299-8153.

CALIFORNIA (NORTHERN)—Exceptional opportunity exists for additional internist with a well-established multispecialty group. Excellent board-certified colleagues with shared call and subspecialty back-up. Academic appointment available. Competitive salary and lucrative benefits. Exclusive location. Contact: Danise Cooper at (800) 776-5776.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

FAMILY PRACTICE

Northern California multispecialty group has immediate opening. Clinical activities involve full range of Family Practice **outpatient and inpatient practice.** Abundant recreational opportunities and small town living. Competitive salary and comprehensive benefit package. CV to: **10978 Donner Pass Rd, Truckee, CA 96161.**

Attention California Breast Cancer Researchers

The Breast Cancer Research Program (BCRP) announces the initiation of its second cycle of research funding, for which approximately $14 million has been appropriated and is available. Any individual or organization in California may submit applications for breast cancer research to be conducted in California. BCRP is soliciting applications from investigators seeking funding for projects in Cycle II priority areas:

- Etiology of Breast Cancer
- Prevention of Breast Cancer
- Innovative Treatment Modalities
- Pathogenesis of Breast Cancer
- Earlier Detection of Breast Cancer
- Innovative Models of Care

Applications are due January 12, 1996, for funds starting June 1, 1996. For copies of the Cycle II call for applications and the complete Application Packet, contact the BCRP office by letter, phone, fax, e-mail or the Internet; or attend one of the information meetings scheduled in early November at various locations around the state.

Breast Cancer Research Program
University of California
Office of the President
300 Lakeside Dr, 12th Fl
Oakland, California 94612-3550
Phone: (510) 987-9884
FAX: (510) 835-4740
Internet: BCRP@UCOP.EDU.
WWW Home Page: http\\www.ucop.edu\srphome\bcrp\bcrphome.html.

BCRP was established by the California Breast Cancer Act of 1993 and funded with the revenue from an increase in the state tobacco tax. In its first grant cycle, the program awarded approximately $19 million to 77 investigators at 22 California institutions. The Cycle I Compendium of Awards is also available from the BCRP office.

CALIF & WEST STATES

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PHYSICIANS WANTED

CALIFORNIA—Emergency Medicine/Family Practice. California Emergency Physicians Medical Group is a partnership of Emergency Medicine and ambulatory care specialists contracting with over 30 Emergency Departments and 10 ambulatory care centers in Northern, Central, and Southern California. We are seeking BC/BP Emergency Medicine and Family Practice Physicians. We offer attractive compensation, ownership, health, disability, and retirement benefits. Send your CV or contact John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

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OPHTHALMOLOGIST: Full- or part-time for busy San Francisco practice. Excellent opportunity. Send CV to: Box 471018, San Francisco, CA 94147 or FAX to: (415) 738-0228.

OREGON COAST: Opportunity for high quality of life, low cost of living on beautiful Oregon coast for BC/BE family practice physician to join multispecialty group at its new satellite location in Bandon. Full spectrum of Family Practice. Competitive compensation package. Send CV or contact Marce Knight, 1900 Woodland Dr, Coos Bay, Oregon 97420; (503) 267-5151, X294; (800) 765-0052.

INTERNAL MEDICINE

CALIFORNIA

NORTHERN CALIFORNIA

EXCELLENT OPPORTUNITY for BE/BC general internist to join a 76-physician multispecialty clinic in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. New internist joining the clinic will quickly become busy as two of the internists in the group will retire during 1996. Looking for someone to start as soon as possible.

Interested parties send CV and three references with phone numbers to: President/CEO, Santa Cruz Medical Clinic, 2025 Soquel Ave, Santa Cruz, CA 95062.

HCR

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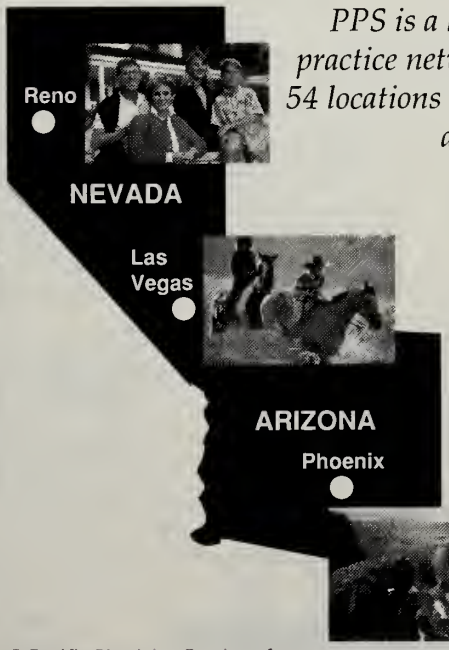

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Or Send CV to Pacific Physician Services ¥ Physician Relations
1826 Orange Tree Lane
Redlands, CA 92374

WASHINGTON STATE—BC/BE FAMILY PHYSICIANS with interest in OB needed to join migrant community health centers in Yakima, Grandview and Walla Walla. All clinics located in rural to urban settings within driving distance of metropolitan areas and outdoor recreational activities. Competitive salary and benefit package. Federal and State loan repayment slots may be available. Contact: Mayling Chin, Recruiting Specialist or Ann Garza, Director of Personnel, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, Washington 98948. Office: (509) 865-5898. FAX: (509) 865-4337.

CALIFORNIA WINE COUNTRY. Sonoma Developmental Center is seeking a BC/BE Internal Medicine physician to provide inpatient care at a long-term care facility serving developmentally disabled individuals. Near the town of Sonoma in California's beautiful Wine Country. Owned and operated by the State of California. Attractive compensation package. Contact Michael Wymore, MD, Medical Director, Sonoma Developmental Center, 15000 Arnold Dr, Eldridge, CA 95431 or call (707) 938-6556, FAX (707) 938-6574.

WESTERN WASHINGTON GENERAL PHYSICIANS AND INTERNISTS. Physicians' salary to $75,000. Internists (BE/BC) salary to $82,776. Western State Hospital is a fully accredited (JCAHO) and certified (HCFA) 1,002-bed hospital serving adult, geriatric, and forensic population. The hospital is associated with the University of Washington. Western currently has a physicians' staff of 54, including 36 psychiatrists and 15 other nonpsychiatric physicians. Excellent benefits, including hospitalization/medical insurance, retirement, vacation estimated equivalence at 30%, plus optional deferred income plan. Send CV to Jerry Dennis, MD; Acting CEO; Western State Hospital; 9601 Steilacoom Blvd SW; Tacoma, WA 98498-7213.

MEDICAL ONCOLOGIST, ABMT-trained, needed for a busy practice. Immediate opening in Nevada. Attractive salary plus. Send CV to Box 305, *The Western Journal of Medicine,* PO Box 7602, San Francisco, CA 94120-7602.

SANTA CRUZ, CA—COASTAL, SOUTH OF SAN FRANCISCO. Seeking part-time GYN, BC/BE practitioner to replace one in two-person busy practice. Available Oct. 1995. Contact Lindsay Johnson, MD, 3275 Aptos Rancho Rd, Aptos, CA 95003, or call (408) 688-8266.

YES, YOU'RE INVITED to tour the sunbelt. . . .Most expenses paid, most evenings and weekends off, and make money while doing it. Just call us and tell us when you'd like to fill a LOCUM TENENS job in the states from California to Florida. We'll do the rest! Call Catalina Professional Recruiters, Tucson, (800) 658-9166, FAX (520) 322-2676, or Phoenix, (800) 657-0354, FAX (602) 433-9548.

EMERGENCY DOCS! Are you ready to give up night shifts and a violent big city environment? **FAMILY DOCS!** Are you burned out with night call, weekend call, and running a small business? If you are not ready to retire but would like a change of pace, consider working in our high-quality minor emergency centers in Boise, Idaho. You will work with Idaho Emergency Physicians, one of the Northwest's premiere emergency/urgent care physician-owned groups. Live within minutes of downhill and cross-country skiing, boating, white water, fishing, and hunting in a dynamic and growing community. We offer a complete financial and benefit package with full administrative support. Send CV to Recruiting Chairman, IEP, 2312 N Cole Road, Suite B, Boise, ID 83704.

PHYSICIANS WANTED? Call (415) 882-3376 to list your openings in WJM.

PRIMARY CARE

OREGON & S.W. WASHINGTON

Northwest Permanente, P.C., a professional group of physicians providing medical services to 380,000 members of Kaiser Permanente in Oregon and Southwest Washington, has full-time and part-time opportunities in general family practice for BC/BE Family Physicians and Internists in Salem and Portland, OR and Longview, WA. In Salem, opportunities exist for Family Physicians or Internists with a special interest or expertise in geriatrics.

Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest and a competitive salary/benefits package. **Forward inquiry and C.V. to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah Street, Suite 100, Portland, OR 97232-2099. EOE.**

KAISER PERMANENTE
Northwest Permanente, P.C.
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Arizona Medical Association, Inc–810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1996, Scottsdale Plaza Resort, Scottsdale.

California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 1-5, 1996, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 20-22, 1996, Steamboat Sheraton, Steamboat Springs.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1996, Sun Valley Inn, Sun Valley, Idaho.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, New Mexico Medical Society Offices, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 25-28, 1996. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 26-28, 1996. Tacoma Sheraton, Tacoma.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1996, Jackson Lake Lodge, Moran.

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ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES: 1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12(3, Suppl):S41-S42. 3. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. 4. Data on file, Protocol CTA 0393, Rhône-Poulenc Rorer Pharmaceuticals Inc. Abstract published in *J Allergy Clin Immunol* 1994;93(1, Pt 2):164.

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(triamcinolone acetonide) Nasal Inhaler

Provides comfortable, prompt relief of allergic rhinitis and effective QD dosing

- *Nasacort remains in the nasal mucosa with no measurable effect on HPA function*[1-3*]
  Duration of acquisition of the PET image was approximately 55 minutes due to ^{11}C decay ($t_{1/2}$ of 20 minutes).[1] *(n=2)*
- *Onset of action as early as 12 hours*[4]
  Maximum benefit generally seen within 3 to 4 days[4]
- *Nasacort provides effective QD dosing flexibility—2 puffs/nostril/day effectively controls symptoms in most patients*
  - *After symptoms have been brought under control, reducing the daily dose to 1 puff/nostril/day is effective in approximately 50% of patients being treated long term*
  - *QD dosing can be increased to 4 puffs/nostril/day if greater effect is desired*

The most commonly reported side effects are headache and nasal irritation, each with an incidence comparable to placebo.

Please see brief summary of prescribing information on adjacent page.

** In doses up to 440 mcg/day.*[3]

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The Western Journal of Medicine

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THE WESTERN JOURNAL OF MEDICINE

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The Western Journal of Medicine

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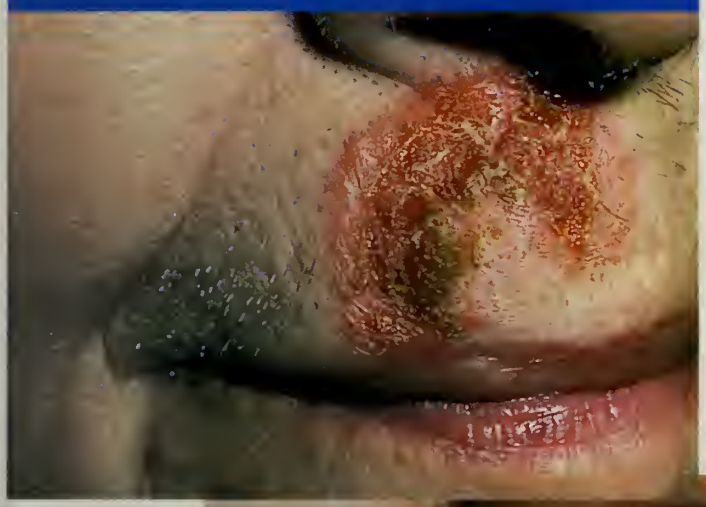
Effective Therapy Right Where You Need It

Presentation:



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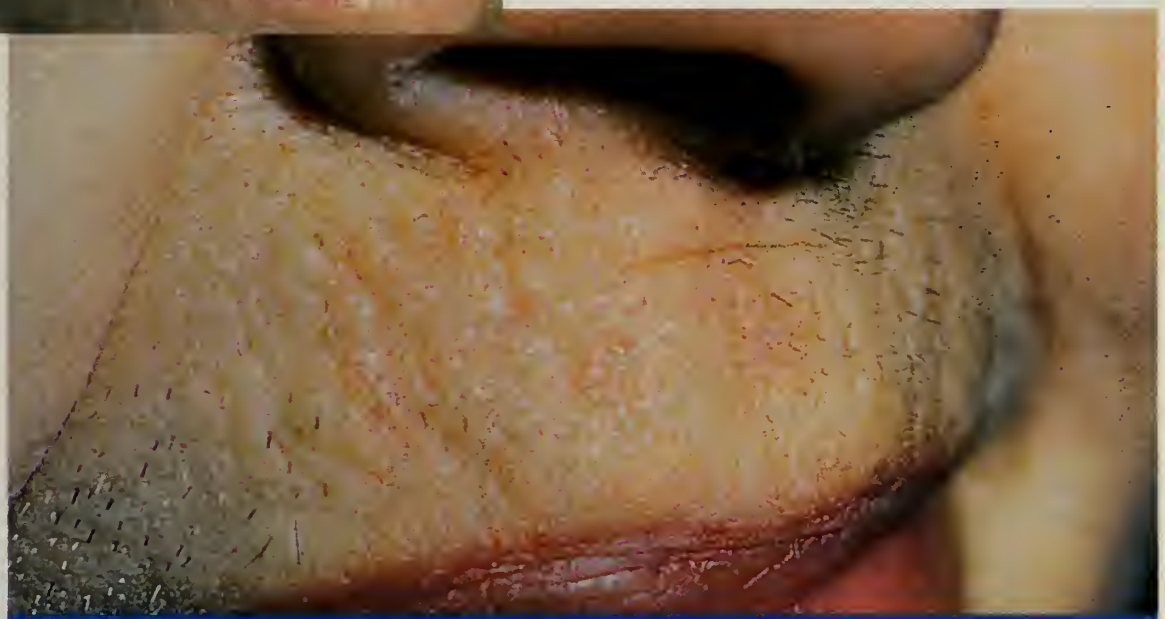

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1. Britton JW, Fajardo JE, Krafte-Jacobs B. Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr.* 1990;117:827-829.
2. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. *Pediatrics.* 1992;89:210-214.
3. Bactroban® prescribing information.

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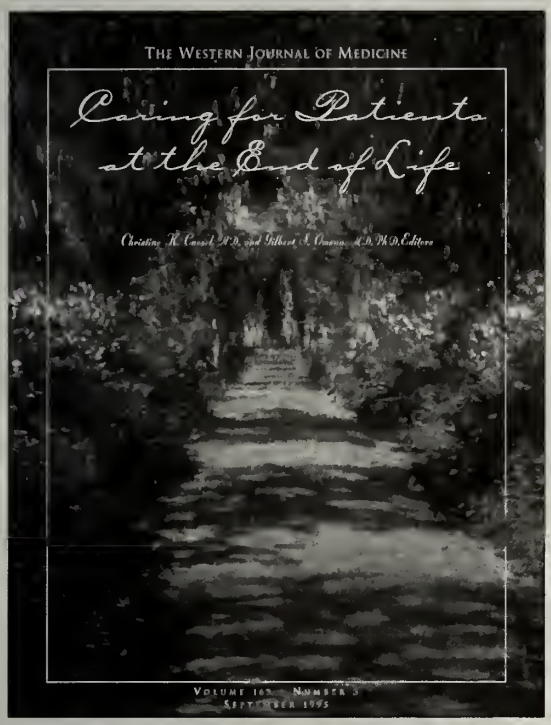

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- The Futility Problem
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- Care of the Family When the Patient is Dying

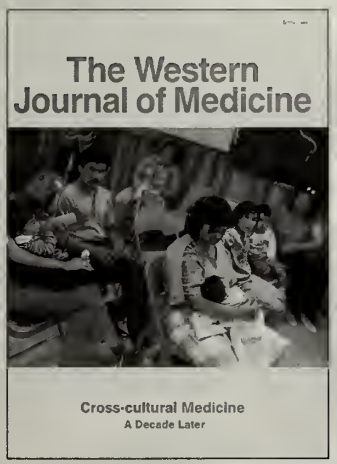
Christine Cassel, MD, & Gilbert S. Omenn, MD, PhD
Special Issue Editors, 1995

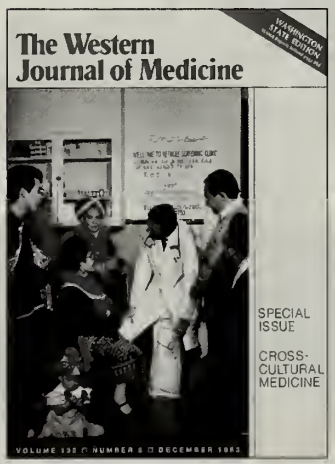
Cross-cultural Medicine —A Decade Later

Ethnic Groups Covered

Chinese-American, East Indian, Afghan, Gypsy, American Indian, Vietnamese, African American, Iranian, Korean American, Laotian, Ethiopian, Russian, Migrant Workers, and French

Judith Barker, PhD
Special Issue Editor, 1992





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SOUTHERN MEDICAL ASSOCIATION

SPRING 1996 CALENDAR

February 16-18	**2nd Annual New Drugs Update: Indications, Interactions, Efficacy and Cost Analysis** Hotel Nikko, Atlanta, GA
March 7-10	**Sixth Annual SEC Sports Medicine Symposium** Fairmont Hotel, New Orleans, LA
March 29-31	**Update on Emergency Medicine & Acute Burn Care** Amelia Island Plantation, Amelia Island, FL
April 26-28	**Common Clinical and Practice Skills: Use and Interpretation** Ritz-Carlton – Buckhead, Atlanta, GA
May 3-5	**Emerging Trends in Infectious Diseases: A Problem-Based Symposium** Sheraton Charleston Hotel, Charleston, SC
May 16-18	**Sixth Annual Current Concepts in Orthopaedics** Omni Inner Harbor Hotel, Baltimore, MD

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LESSONS FROM THE PRACTICE

TOPICS IN PRIMARY CARE MEDICINE

OTHER FEATURES

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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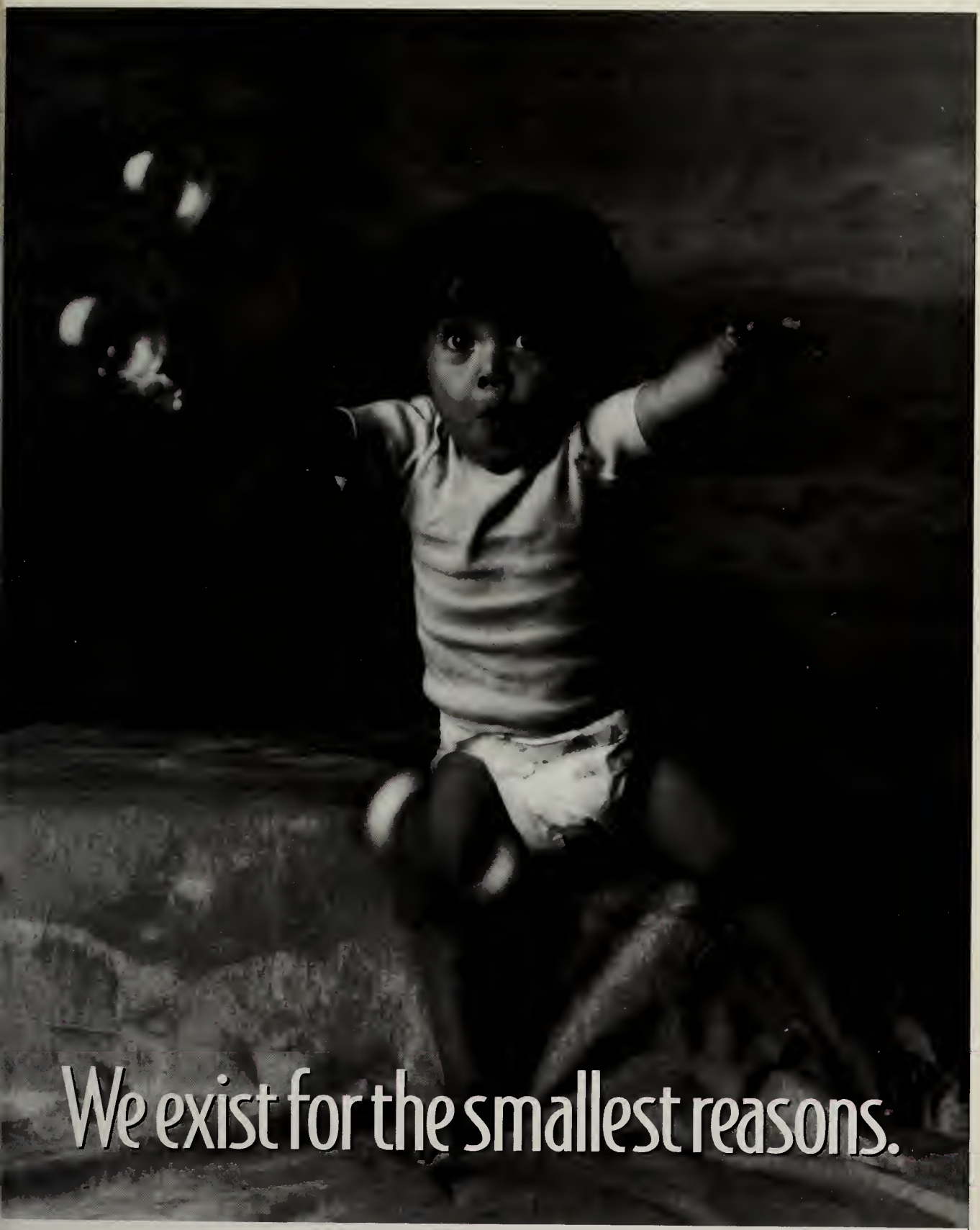

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 29—**The Role of Tissue ACE in the Management of Congestive Heart Failure.** University of Arizona College of Medicine at the Westin La Paloma, Tucson. Wed. Contact: U of A.

December 1-2—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at the Westin La Paloma, Tucson. Wed. Contact: U of A.

December 1-2—**Pediatric Trauma, Special Equipment, Difficult Airway Management.** International Trauma Anesthesia and Critical Care Society at the Phoenician Resort, Scottsdale. Fri-Sat. Contact: (800) 875-2525.

December 1-2—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at the Hyatt Regency, Scottsdale. Fri-Sat. Contact: (800) 421-3756.

December 2—**ENT for the Specialist**. Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 11-14—**6th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Thurs-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 13—**High-Dose Chemotherapy & Bone Marrow Transplantation in the Management of Breast & Ovarian Cancer.** University of Arizona College of Medicine at the Red Lion's La Posada Resort, Scottsdale. Sat. Contact: U of A.

January 16-20—**Phoenix Surgical Society—24th Annual Meeting**. Phoenician Resort, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

January 19-21—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 19-21—**The Scottsdale Headache Symposium; Headache and Face Pain.** American Association for the Study of Headache at the Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: (609) 845-1720.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 11-15—**International Congress IX on Endovascular Interventions**. Arizona Heart Institute and International Society for Endovascular Surgery at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: Erika Scott, (602) 266-2200.

February 12-16—**5th Annual Psychopharmacology Review**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

February 15-17—**Mayo Interactive Surgical Symposium**. Mayo Foundation at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Trish Gean, (602) 301-8323.

February 16-18—**Arizona Society of Anesthesiologists: Anesthesia for the 90s.** University of Arizona College of Medicine at the Doubletree Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: U of A.

February 17—**Ninth Epilepsy Update: Seizures at All Ages.** University of Arizona College of Medicine at the Austin La Paloma Resort, Tucson. Sat. Contact: U of A.

February 19-22—**State-of-the-Art Echocardiography (1626).** American College of Cardiology at Tucson. Mon-Thurs. Contact: (800) 257-4739.

February 22-24—**5th Biennial Geriatric Medicine Update and Certification Exam Review Course.** University of Arizona College of Medicine at The Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

March 3-6—**10th Annual Magnetic Resonance Imaging Conference.** St Joseph's Hospital and Medical Center and Barrow Neurological Center at the Phoenician Resort, Scottsdale. Sun-Wed. Contact: (602) 406-3067.

March 7-9—**23rd Annual Symposium: Recent Advances in Neurology & Neurosurgery.** St Joseph's Hospital and Medical Canter and Barrow Neurological Institute at the Phoenician Resort, Scottsdale. Thurs-Sat. Contact: (602) 406-3067.

March 7-10—**19th Annual Mid-Winter Symposium: Advances in Obstetrics & Gynecology**. Maricopa Medical Center and Phoenix OG/GYN at the Radisson Resort Hotel, Scottsdale. Thurs-Sun. Contact: Cathy Clifton, (602) 267-5366.

March 10-14—**Radiology in the Desert; Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at the Marriott's Camelback Inn, Scottsdale. Sun-Thurs. Contact: Vivian Woods, (313) 763-1400.

March 13-16—**International Conference on the Adjuvant Therapy of Cancer.** University of Arizona College of Medicine at the Wyndham Paradise Valley Resort, Scottsdale. Wed-Sat. Contact: U of A.

March 21-23—**Ophthalmic Reviews 1996: Oculoplastics from Coast to Coast.** Mayo Clinic-Scottsdale at the Radisson Resort, Scottsdale. Thurs-Sat. Contact Trish Ghan, Mayo Clinic-Scottsdale.

March 28-30—**5th Annual Urogynecology and Disorders of the Female Pelvic Floor.** Mayo Clinic-Scottsdale at The Points Hilton Resort at Tapatio Cliffs, Phoenix. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

April 9-13—**New Frontiers in Pain.** Maricopa Medical Center at the Radisson Resort Hotel, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

April 10-13—**21st Annual Primary Care Update.** University of Arizona College of Medicine at the Tucson Hilton East, Tucson. Wed-Sat. Contact: U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 30-February 3— **34th Annual Scientific Session of the Western Society of Allergy and Immunology**. Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, P.O. Box 1122, Roanoke, TX 76262. (817) 491-2616.

(Continued on Page 428)


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CONTINUING MEDICAL EDUCATION

(Continued from Page 426)

ANESTHESIOLOGY

January 10-13—**UCSD Anesthesia Update**. UCSD at Hotel del Coronado. Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 11-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. 2 wks. 20 hrs. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City, CA 94404. (800) 345-3691.

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 26-29—**5th John J. Bonica Hawaii Pain Conference**. Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

December 8-10—**13th Annual Advances in Heart Disease: An International Perspective.** American College of Cardiology at San Francisco. Fri-Sun. 16.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

December 9—**Cardiac Therapeutics.** USC at Ritz-Carlton, Laguna Niguel. Sat. 8 hrs. $75. Contact: USC.

January 26-28—**Clinical Nuclear Cardiology: Case Review With the Experts**. Cedars-Sinai Medical Center at Los Angeles. Fri-Sun. 17.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

March 2-9—**Update: Controversies in Cardiovascular Disease.** UCSD at Stouffer Wailea Resort, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

April 25-27— **Sixth Annual Symposium on Coronary Stenting.** Scripps Clinic & Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

December 3-8—**16th Annual Current Concepts in Emergency Care**. American College of Emergency Physicians at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269.

December 11-15—**Emergency Medicine Symposium II**. UCSD at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 15-19—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 18-20—**California Trauma Conference**. UCD at Hyatt Regency, Sacramento. Thurs-Sat. 17 hrs. $425. Contact: UCD.

February 24-March 2—**Pediatric Emergencies**. UCSD at Royal Lahaina, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

March 18-22—**Emergency Medicine Symposium II**. UCSD and BSB at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

December 7-9—**Clinical Care of the AIDS Patient**. UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 24 hrs. $395. Contact: UCSF.

December 9-11—**Bone Mass Management in Osteoporosis and Other Bone Diseases.** National Osteoporosis Foundation at the Biltmore Hotel, Los Angeles. Sun-Mon. 14 hrs. Contact: NOF, 1150 17th St NW, Ste 500, Washington, DC 20036-4603. (202) 223-2226.

January 19-21—**Dermatology for the Non-Dermatologist**. Continuing Medical Education Associates at Hyatt Regency La Jolla, San Diego. Fri-Sun 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

January 20-27—**Sports Medicine.** UCSD at Royal Waikoloan, Kona, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

January 22-24—**Ophthalmology and ENT for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Primary Care Dermatology**. UCSD at Hilton Beach and Tennis Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: UCSD.

February 1-3—**Neurology for the Non-Neurologists.** UCSD. Thurs-Sat. 21 hrs. $500. Contact: UCSD.

February 16-18—**Office Gynecology and Women's Health for the Primary Care Physician**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

March 20-22—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 15 hrs. $325. Contact: UCSF.

April 1-4—**Primary Care in Paradise: Maui 1996.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla 92037. (619) 554-8556.

April 18-21—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hilton Beach and Tennis Resort, San Diego. Thurs-Sun. 20 hrs. $495. Contact: CMEA Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

April 27—**29th Society of Teachers of Family Medicine Annual Spring Conference.** AAFP and Society of Teachers of Family Medicine at The Hyatt Regency at Embarcadero Center, San Francisco. Sat-Wed. Contact: Ray Rosetta, Director of Meetings and Programs, The Society of Teachers of Family Medicine (800) 274-4512.

May 17-21—**Essentials in Primary Care**. Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

February 9-10—**Advances in Diagnosis and Treatment of Splenic Disorders.** Cedars-Sinai Medical Center at Hotel Sofitel Los Angeles. Fri-Sat. 11.5 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Room 2211, Los Angeles 90048. (310) 855-2937.

February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in La Jolla. Sat. 7 hrs. $ 140. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

February 14-16—**29th Annual Recent Advances in Neurology**. UCSF at Sheraton Palace Hotel San Francisco. Wed-Fri. 15 hrs. $375. Contact: UCSF.

February 17-22—**Topics and Advances in Internal Medicine**. UCSD at San Diego Marriott. Sun-Thurs. 50 hrs. $595. Contact: UCSD.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 825-6774.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 428)

March 15-21— **Internal Medicine 1996.** Continuing Medical Education Associates at the Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

April 11-13—**Recent Advances in Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. Contact: UCSD.

April 20—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Saturday, 6 hrs. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Rd., La Jolla, 92037. (619) 554-6310.

May 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

MANAGED CARE

January 19-21—**Neurosurgery, Government, and Managed Care: Adapting to a Changing Environment.** California Association of Neurological Surgeons at Hyatt Regency Hotel, Sacramento. Fri-Sun. Contact: Janine Tash, CA Assoc. of Neurological Surgeons. (916) 443-0236.

January 26-27—**Advances in Pulmonary Medicine: Medical Care to Managed Care.** California Thoracic Society at Le Meridien San Diego at Coronado. Fri-Sat. 10 hrs. Contact: California Thoracic Society, 202 Fashion Lane #219, Tustin, 92680. (714) 730-1944.

NEPHROLOGY

January 31-February 3—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Regency on the Bay San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

December 1-2—**Controversies in Hormones, Menopause, and Breast Cancer.** MMI/UCI Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

December 7-10—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's, Las Vegas. Thurs-Sun. $295. Contact: Center for Continuing Medical Education, University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

February 10-13—**51st Annual Postgraduate OB/GYN Assembly.** Obsterical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Sat-Tues. 22 hrs. Contact: Director, 5820 Wilshire Blvd #500, Los Angeles 90036. (213) 937-5514.

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

January 29-February 2—**Occupational & Environmental Medicine I.** UCSF at Miyako Hotel San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF

ONCOLOGY

December 3—**Tumor & Tumor-Like Conditions of the Bone.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sun. 8 hrs. Contact: Anne E. Chism CTTR, c/o Loma Linda University, School of Medicine, Dept. of Pathology, 11021 Campus Ave, AH 335, Loma Linda 92350. (909) 824-4788.

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Articles

Unintentional Deaths From Carbon Monoxide Poisoning in New Mexico, 1980 to 1988
A Comparison of Medical Examiner and National Mortality Data

RONALD L. MOOLENAAR, MD; RUTH A. ETZEL, MD, PhD; *and* R. GIBSON PARRISH, MD, *Atlanta, Georgia*

Carbon monoxide was the number 1 cause of poisoning deaths in the United States from 1980 through 1988, with the highest rates reported in the western states. We studied unintentional deaths from carbon monoxide poisoning in New Mexico during this period using the multiple-cause mortality files from the National Center for Health Statistics (NCHS) and data from the New Mexico Office of the Medical Investigator (OMI). We compared the nationally available NCHS data with the more detailed OMI data to determine the sensitivity of NCHS data for the surveillance of this preventable cause of death. The NCHS data were 88% sensitive in identifying deaths from unintentional carbon monoxide poisoning and had a positive predictive value of 81% when compared with OMI data. Half of the unintentional carbon monoxide-related deaths were attributable to a home heating mechanism of some sort, 46% involved motor vehicle exhaust, and at least 42% were associated with alcohol use. We conclude that available NCHS data are a sensitive source of surveillance information about unintentional deaths from carbon monoxide poisoning. Additional details about specific deaths can be obtained from medical examiner files when needed.

(Moolenaar RL, Etzel RA, Parrish RG: Unintentional deaths from carbon monoxide poisoning in New Mexico, 1980 to 1988—A comparison of medical examiner and national mortality data. West J Med 1995; 163:431-434)

Unintentional carbon monoxide poisoning claimed 11,547 lives in the United States from 1979 through 1988, and it was the number 1 cause of poisoning deaths during that period. Western states tended to have higher rates of death from this cause, with Alaska (1), Wyoming (2), Montana (3), Nebraska (4), and New Mexico (5) having the top five death rates for all the states. Colorado, Utah, and Idaho also had unintentional carbon monoxide poisoning death rates above the median rate for the United States.[1]

In the United States, two major sources of data have been used in epidemiologic studies of mortality from unintentional carbon monoxide poisoning: the National Center for Health Statistics (NCHS) multiple-cause mortality-data files[2] and medical examiner records.[3-5] The NCHS annually compiles these multiple-cause mortality-data files from death certificates completed in the United States. This method of quantifying rates of unintentional death due to carbon monoxide poisoning is convenient and could be used for each state, but the sensitivity of these data files in identifying true cases of unintentional carbon monoxide-related death has not been determined. The second source used to study unintentional carbon monoxide-related deaths, medical examiner records, allows further investigation of the cause and circumstances of death.[3-5] Medical examiner or coroner files are usually detailed and reliable, but are not readily available in every state. They are particularly well suited for studying unnatural, unintentional deaths due to carbon monoxide poisoning because all such deaths should have been investigated by the medical examiner or coroner, and often an autopsy has been done.[6] The NCHS data have been compared with medical examiner files in studies of deaths due to injuries.[7,8]

We studied mortality from unintentional carbon monoxide poisoning in New Mexico because New Mexico has a high death rate from this cause[1] and because mortality data were available both from NCHS multiple-cause mortality files and from the state medical examiner's office. The purpose of this investigation was to determine the sensitivity of NCHS mortality data for quantifying unintentional carbon monoxide-related deaths and to describe the epidemiology of this preventable cause of death in New Mexico.

Methods

We looked first at the NCHS multiple-cause mortality data for 1980 through 1988. Information in these files is

From the Division of Environmental Hazards and Health Effects, Centers for Disease Control and Prevention, Atlanta, Georgia.
Reprint requests to Ronald L. Moolenaar, MD, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop C-08, Atlanta, GA 30333.

ABBREVIATIONS USED IN TEXT

ICD-9 = *International Classification of Diseases*, 9th revision
NCHS = National Center for Health Statistics
OMI = Office of the Medical Investigator

abstracted from death certificates, which are gathered first at the local level, then at the state level, and finally at the federal level by NCHS. After coding the data, NCHS makes computerized files available to the general public. For each death, *International Classification of Diseases*, Ninth Revision (ICD-9),[9] codes are listed for the underlying cause of death and as many as 20 contributing conditions. Using the NCHS files, we selected death records of New Mexico residents who died from 1980 through 1988 in New Mexico. We then searched these records for those deaths with the ICD-9 code N986 (toxic effect of carbon monoxide) listed as either the underlying cause of death or as a contributing condition. From these, we selected deaths with any of the following codes: E811 through E813, E815, E816, E818, E819, E825, E838, E841, E844, E867, E868.0 through E868.9, E869.8, or E869.9. These external-cause or "E" codes could be listed as either the underlying cause of death or a contributing condition and further characterize deaths due to external or environmental factors. Finally, we excluded carbon monoxide deaths due to suicide and self-inflicted injury (E950 through E959), homicide and injury purposefully inflicted by other persons (E960 through E969), injury undetermined whether accidentally or purposefully inflicted (E980 through E989), injury caused by fire and flames (E837, E890 through E899), burns (E940 through E949), and injuries caused by explosives (E923). Many of the fire- and explosion-related deaths may have been unintentional and carbon monoxide-related, but as public health problems, their prevention falls into the category of preventing fires and explosions rather than preventing carbon monoxide poisoning.

This case definition—including the inclusion and exclusion criteria outlined above—has been used previously in conjunction with NCHS multiple-cause mortality data to study unintentional carbon monoxide poisoning deaths.[1] To determine the sensitivity of NCHS multiple-cause mortality data in identifying carbon monoxide poisoning as just defined, we compared them with data obtained from the New Mexico medical examiner's office, the Office of the Medical Investigator (OMI).

We searched data from the files of the OMI from 1980 through 1988 for deaths that occurred in New Mexico to persons whose state of residence was either listed as New Mexico or was unlisted. We searched these records for those deaths coded by the OMI as due to, or involving, carbon monoxide (coded as C12). We then searched these deaths for cases with a manner of death code of A37, which signifies a death due to nonabusive inhalation. This code excludes deaths due to suicide, homicide, fires, and explosions, as well as deaths for which the manner of death is unknown. Thus, these two codes, C12 and A37, were used to define deaths possibly from unintentional carbon monoxide poisoning in the OMI files. Finally, we reviewed the circumstances of each death as described in the medical examiner's record and selected only those deaths for which the narrative description of the circumstances of death was consistent with unintentional carbon monoxide poisoning.

TABLE 1.—*Unintentional Deaths Attributed to Carbon Monoxide (CO) Poisoning in New Mexico from 1980 through 1988 as Recorded in Files of the Office of the Medical Investigator (OMI) or in the National Center for Health Statistics (NCHS) Multiple-Cause Mortality Files*

	OMI Deaths, No.		
NCHS Deaths	*CO-Related*	*Other**	*Unmatched†*
CO-related	60	14	1
Other*	8		
Unmatched†	6		

*"Other" refers to cause of death recorded as unintentional CO poisoning in 1 data file, but recorded as something other than an unintentional CO-related death in the other data file.
†"Unmatched" refers to CO-related deaths recorded in 1 file that could not be matched to any death in the other file on the basis of age, sex, and month, day, and year of death. The unmatched NCHS death was listed as a nonresident death in the OMI data set.

Using age, sex, and month, day, and year of death, we matched deaths listed in the NCHS multiple-cause mortality files as being from unintentional carbon monoxide poisoning with carbon monoxide-related deaths from the OMI files. We manually reviewed those deaths that matched on sex and month and year of death but did not match on age or day of death; we considered the deaths to be matches if only one of these variables prevented a perfect match. We then calculated the sensitivity and the predictive value of the NCHS data in identifying unintentional carbon monoxide-related deaths that were also identified in the OMI files. Finally, we performed a more in-depth review of the OMI records to characterize the victims of carbon monoxide poisoning and the circumstances surrounding their deaths. We used United States census data from 1980 to calculate mortality rates.

Results

Using NCHS multiple-cause mortality-data files, we found 75 unintentional carbon monoxide-related deaths occurring in New Mexico among residents of the state during 1980 through 1988 (Table 1). Of these, 74 were matched to deaths in the OMI files. The unmatched death was labeled a nonresident death in the OMI files. Using the OMI files, we found 74 deaths from unintentional carbon monoxide poisoning occurring in the state among residents during this same time period. Of these, 68 were matched to deaths in the NCHS data. We found 60 unintentional carbon monoxide-related deaths present in both data sets. Seven of these were matched manually: six mismatched only on age, and one mismatched only on day of death.

Eight matched deaths were labeled as unintentional carbon monoxide-related deaths in the OMI files but had other diagnoses in the NCHS files. Three of these deaths were classified in the OMI files as being unintentional carbon monoxide-related deaths, but the underlying

cause of death in the NCHS files was "unknown" (ICD-9 code, 799.9). In five cases, there appeared to be coding errors in the NCHS files.

Of the 74 matched deaths, 14 were labeled as unintentional carbon monoxide-related deaths in the NCHS files but were listed as having other causes in the OMI records. Of those deaths, the medical examiner case reports revealed that 5 were due to fires, 4 were suicides, 3 were due to motor vehicle accidents, 1 was attributed to asthma, and another to heart disease.

Of the 68 matched deaths from unintentional carbon monoxide poisoning confirmed by the OMI data, the NCHS data were successful in identifying 60, for a sensitivity of 88.2%. The probability that 1 of the 74 matched deaths identified from NCHS data as due to unintentional carbon monoxide poisoning could be confirmed as such with OMI data was 81.1% (positive predictive value).

To gain further insight into the demographic characteristics and causes of death for the 74 people whose deaths were identified as unintentional carbon monoxide-related deaths by the OMI (68 matched and 6 unmatched), we reviewed the circumstances of death for each decedent. Of the 74 people, 55 (74%) were male. Their median age was 35 years, with a range of 4 months to 87 years. More than half (55%) were white, 27% Hispanic, 11% American Indian, and 7% African American. The annual death rate per 100,000 persons was 2.41 for blacks, 0.83 for American Indians, 0.47 for Hispanics, and 0.46 for whites. We noted a pronounced seasonal trend, with the greatest number of deaths occurring in the winter months (Table 2). The number of deaths has declined in recent years (Table 3).

Half of the deaths (37) were due to a home-heating mechanism of some sort, and 34 (46%) were caused by motor vehicle exhaust. Two thirds of the deaths (68%, 50 persons) occurred in a residential setting, in either a home or a garage. A total of 34 deaths (46%) occurred in carbon monoxide poisoning episodes that involved other persons, some of whom survived. In all, 7 deaths (9%) resulted from the use of makeshift heating devices such as hibachi grills (2), a lantern (1), an army helmet filled with charcoal (1), or buckets used for burning wood indoors (3). Outside the home or automobile, deaths also occurred in such places as the workplace (2), in the back of a camper (3), in a motel (1), and in recreational settings such as a van (1) or houseboat (2).

TABLE 2.—*Unintentionol Deoths Due to Corbon Monoxide Poisoning in New Mexico From 1980 to 1988 os Recorded in the Files of the Office of the Medicol Exominer by Month of Occurrence*

Month	Deaths, No.
January	13
February	9
March	7
April	5
May	1
June	0
July	4
August	2
September	1
October	8
November	11
December	13
Total	74

TABLE 3.—*Unintentionol Deoths Due to Carbon Monoxide Poisoning in New Mexico from 1980 to 1988 os Recorded in the Files of the Office of the Medicol Investigotor by Yeor of Occurrence*

Year	Deaths, No.
1980	10
1981	11
1982	7
1983	11
1984	13
1985	8
1986	6
1987	5
1988	3
Total	74

A detectable alcohol concentration of 0.1 grams per liter (0.01 grams per dl) or greater was present in either antemortem or postmortem blood specimens of 31 (42%) of the decedents. In 17 of these 31, the level was 1.0 grams per liter (0.1 grams per dl) or greater. Of the 31 deaths associated with alcohol consumption, the median age was 33 years, 26 (84%) occurred among men, 18 (58%) were associated with automobile exhaust, and 10 (32%) were related to the use of a heating device.

Discussion

In this study, we compared the use of NCHS data with that of OMI data for the surveillance of unintentional carbon monoxide-related deaths in New Mexico. Compared with the OMI data, the NCHS data had a sensitivity of 88.2% and a positive predictive value of 81.1% for identifying deaths from this cause. The NCHS data provide national coverage and are available within two to three years. Although not available for all states, medical examiner or coroner data are usually more detailed and can be used to supplement NCHS data with more specific information about the characteristics of a decedent and the circumstances of death. By using data from two sources, as was done in this study, researchers conducting descriptive epidemiologic studies can add to the existing body of knowledge about the causes and possible means of preventing unintentional carbon monoxide-related deaths in a particular region.

Other studies of unintentional carbon monoxide poisoning done in other states and in the United States as a whole have revealed that unintentional carbon monoxide poisoning tends to occur in the colder months of the year, and states with cold winters or with high-altitude areas have higher mortality rates in general. Motor vehicle exhaust is typically the most common cause of death, but many deaths occur in the home, often

due to old or poorly ventilated heating systems. Men have higher carbon monoxide-related death rates than women, and death is frequently associated with the use of alcohol.[1,3-5]

The earliest symptoms of poisoning from carbon monoxide are nonspecific and may resemble a flulike illness, with headache, fatigue, and mild central nervous system symptoms of drowsiness or lethargy. Early evidence of poisoning is commonly overlooked, allowing exposure to continue insidiously. With further exposure, somnolence, seizures, coma, and eventually death may result. In cases of severe nonfatal poisoning, residual neurologic impairment may occur, and this may be delayed by several weeks after the original insult. Deaths from carbon monoxide poisoning may occur in clusters and often involve otherwise healthy persons; in retrospect, these deaths are usually preventable. Little information exists regarding the occurrence of nonfatal poisonings, and it has been hypothesized that a substantial amount of morbidity from carbon monoxide poisoning remains undiagnosed.[10]

The cause of death in many cases of carbon monoxide poisoning can be attributed to faulty equipment or a lack of awareness of risk. Proper installation and regular maintenance of home-heating appliances, cleaning of obstructed chimneys, and careful attention to ventilation during the use of butane and kerosene space heaters, wood stoves, and charcoal grills will reduce risk. In many states, the local gas company will check the heating system of a home for carbon monoxide leaks at little or no charge.

Education of both health professionals and the public is also essential to prevent such deaths. Educational efforts should be directed toward those at highest risk, including young male drivers and the elderly or others who live in homes with old heating systems. The health risk of running motor vehicles in closed spaces needs to be reemphasized, particularly among young male drivers. The relation between alcohol consumption while using a motor vehicle and risk for carbon monoxide poisoning also needs further emphasis, perhaps in driving education courses.

Physicians need to be aware of the classic signs and symptoms of carbon monoxide poisoning when seeing patients at risk for this problem. In severe cases, treatment with hyperbaric oxygen may improve the chances of survival. Prevention education may be particularly timely in the autumn before the cold weather months and seasonal increases in carbon monoxide poisoning occur.

Affordable carbon monoxide detectors for residential use, which have been certified according to standards set by Underwriters Laboratories, are now available.[11] These may eventually be substantially cost-effective in preventing carbon monoxide poisoning deaths similar to the way smoke detectors have prevented deaths from residential fires.[12]

Acknowledgment

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Articles

Drugs, Poverty, Pregnancy, and Foster Care in Los Angeles, California, 1989 to 1991

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To determine the characteristics and childbearing histories of women whose infants entered foster care in Los Angeles County, we examined the cases of 1,155 drug-using women whose infants were removed from them at birth and 236 non–drug-using women whose infants were also removed at birth by court order (July 1989 through March 1991). All of the women were indigent, and less than half had graduated from high school. The drug-using women frequently had criminal records, and more than a quarter were homeless. Many comparison women had mental health problems, and some (16.7%) were teenagers under court custody.

Overall, 80% of all the children born to both groups of women were under court jurisdiction. Data obtained after study infants' births on 926 drug-using women observed for 18 months revealed that 22% had borne another infant who was placed in foster care; half of these infants had a positive drug immunoassay. Of the 185 non–drug-using women with 18-month follow-ups, 7.6% had borne another child who was in foster care. The magnitude of the repeated childbearing recorded among both groups of women in this study shows that preventive programs including family planning, mental health services, and drug prevention or rehabilitation programs have not reached this population.

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There is a growing awareness of the acute medical consequences of maternal drug use during pregnancy and the subsequent effects on infants with exposure to street drugs in utero.[1-13] Some cross-sectional studies have described women who abuse street drugs in relation to ethnicity,[14] physical and mental health,[15-17] use of prenatal care services,[18,19] obstetrical risks,[20,21] complications of pregnancy,[22-30] homelessness,[31,32] and risk of the acquired immunodeficiency syndrome.[33-36] A few reports have described the inadequacy of drug rehabilitation programs for pregnant drug-using women.[37-41] Others have delineated the increased costs of caring for infants with exposure to street drugs in utero,[42-45] problems with foster care placement,[46] and the subsequent effects on the child welfare system.[47-49] No published reports have yet focused on mothers of infants exposed to street drugs in utero who become dependents of the court, their childbearing histories, and the number of their children relative to other children in foster care.

In Los Angeles, the Department of Children and Family Services (DCFS) implements the directives of the Juvenile Court of Los Angeles County. The department's responsibilities include supervising children who are placed with parents and relatives or who have been removed from parents and are in protective custody with relatives or in foster care. Over the past decade, there has been a dramatic increase in DCFS's official caseload of infants with exposure to street drugs in utero. During calendar year 1981, there were 132 newborn infants with a positive drug toxicologic screen referred to DCFS directly from hospitals. During 1989, DCFS reported that 200 infants per month with prenatal exposure to drugs were referred directly from hospitals and either became dependents under the jurisdiction of the court or were placed under its supervision—that is, the infant remained in its mother's custody with DCFS staff monitoring the child's care.[50] In 1993 that number grew to 300 infants per month, nearly a 3,000% increase over the 1981 rates.[51]

In mid-1989, we began a study to determine the effects on DCFS of infants infected with the human immunodeficiency virus (HIV), including the effects on the staff who supervised the foster care services for these infants. At that time, the serologic status of the infants referred to the court was frequently unknown. In examining the infant records of DCFS for this study, it became apparent that, although the number of identified HIV-infected infants was small, the vast majority of

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ABBREVIATIONS USED IN TEXT

AFDC = Aid to Families with Dependent Children
DCFS = Department of Children and Family Services
HIV = human immunodeficiency virus

infants removed from their mothers at birth and referred to the Juvenile Court were born to drug-using women who had several other children who were already under the court's jurisdiction. In the absence of information describing the reproductive history of these women and the number of their children under the court's supervision, we collected data to assess the extent of the "repeated pregnancy" phenomenon and its implications.

In this report, we present data on the characteristics and childbearing histories of a sample of 1,155 drug-using women whose newborn infants exposed to street drugs in utero were referred to the Juvenile Court of Los Angeles County and a group of 236 women who were not officially labeled as drug users at the time of delivery, but whose infants were also referred to the court before hospital discharge.

Sample and Methods

Data were collected on a total of 1,391 women during a 20-month interval from July 1989 through March 1991. Each month, a list of women whose infants were referred to the DCFS at birth was reviewed by project staff. We randomly selected a sample of 60 (30%) of the 200 drug-using women on each of the monthly lists of women whose infants had a positive drug immunoassay at birth or whose maternal or neonatal behavior demonstrated drug exposure or withdrawal. A total of 1,155 women was selected over the 20-month period. During this same interval of time, we also enrolled all women (n = 236) classified as non–drug-users by inspection of their DCFS records whose infants were also removed from them by the Juvenile Court before hospital discharge. Although some women in this group may have used drugs during their pregnancies, the detailed social work evaluations conducted before and after delivery classified them as "non–drug-using women at birth."

No women or children were directly contacted or interviewed. This study was sanctioned by a court order from the Presiding Judge of the Juvenile Court of Los Angeles County and approved by the Human Subjects Protection Committee of the University of California at Los Angeles.

Data Collection

Court and DCFS records, including the results of drug toxicologic screens of infants' urine, were reviewed to abstract information related to the women's demographic and personal characteristics, including family background, education, work history, marital status and living arrangements, drug-use history, physical and mental health status, criminal history, drug treatment and rehabilitation, number of children, dates of previous children's births, and whether or not each previous child (younger than 18 years) was under court or DCFS supervision at the time of the woman's entry into the study (1989 to 1991).

Experienced retired social workers who had been in supervisory positions at the DCFS requisitioned and read each record to abstract the desired information. All records were reviewed a second time by the project field director, who found 96% agreement on the total set of items. Information for some variables was not always available in the records (reduced numbers indicated in Tables 1 and 2).

These data, most of which are nominal or ordinal, were obtained from social workers' documentation based on interviews with the women, their relatives, and a review of hospital records. No opportunities were available to assess the validity of the data presented here because, in most cases, that would have required interviewing the women. When we reviewed the hospital records of 612 of the drug-using women's infants, however, we found high correlations between DCFS and hospital information on a number of infant variables (M.A.L., B.L., "Birth Weights of Infants of Drug-Using Women at High Risk for HIV Infection," unpublished data, January 1994).

Data Analyses

Information on the women's sociodemographic, health status, and drug-using characteristics, sexual and criminal activities, and their childbearing histories was examined for the total sample and for each group separately using simple descriptive statistics. Because contrasts between the two subpopulations of women with infants under court custody or DCFS supervision were also of interest, we used χ^2 tests to assess differences in categorical measures between the two samples and t and Wilcoxon two-sample tests to detect differences in continuous measures.

Results

Table 1 describes the sociodemographic characteristics of these women, including their living arrangements, overall and by group, and Table 2 displays their history of prenatal care, mental health status, sexual history, and interaction with the justice system. Figure 1 shows the proportion of all children born to the drug-using women who were under court jurisdiction or supervision.

Sociodemographic Characteristics

As Table 1 shows, the women had an average age of 27 years, and the drug-using women were somewhat older. There was no significant difference in the number of other children they had ($P > .05$ for both t and Wilcoxon 2-sample tests); the overall average was 3.2 children.

There were differences in ethnicity among the two groups of women. Nearly two thirds of the drug-using women were African American, whereas more than a

TABLE 1.—*Sociodemographic Characteristics of Drug-Using and Non–Drug-Using Women Whose Infants Were Referred to the Juvenile Court of Los Angeles County Before Hospital Discharge*

Women's Chorocteristics	*Drug-Using Women (n = 1,155)*	*Non–Drug-Using Women (n = 236)*	*Totol*
Mean age, yr*	28.2	24.0	27.4
Other children, mean No.	3.3	2.4	3.2
Ethnicity, %*			
African American	63.6	41.5	59.8
Latina	19.1	35.2	21.9
White	15.7	20.0	16.4
Income	(n = 905)	(n = 185)	(n = 1,090)
< $5,000 per year	97.0	94.6	96.6
Employment, %	(n = 1,022)	(n = 220)	(n = 1,242)
Full- or part-time	2.7	6.4	3.4
AFDC, %*	(n = 1,024)	(n = 217)	(n = 1,241)
Receiving	47.9	23.0	43.5
Raised by, %†	(n = 941)	(n = 186)	(n = 1,125)
Mother only	39.0	24.0	36.5
Residence, %*	(n = 969)	(n = 200)	(n = 1,169)
Born in USA	96.0	77.0	92.7
Grew up in LA County	69.4	57.0	67.2
Education	(n = 899)	(n = 174)	(n = 1,073)
High school graduate	41.4	28.2	39.2
Marital status, %*	(n = 985)	(n = 214)	(n = 1,199)
Never married	68.7	68.7	68.7
Married to infant's father	9.0	16.4	10.3
Living arrangements, %*	(n = 1,117)	(n = 230)	(n = 1,347)
Alone	14.7	7.8	13.5
Homeless	28.7	11.7	25.8
Incarcerated	4.9	1.7	4.4
Infant's father	16.6	17.8	16.8
Relatives/friends	33.7	25.2	32.2

AFDC = Aid to Families with Dependent Children

*Group differences are significant at the .001 level using 2-tailed χ^2 tests for categorical variables and 2-tailed *t* tests for continuous variables.

†Group difference is significant at the .01 level using the 2-tailed χ^2 test.

third of the non–drug-using women were Latina. There were concomitant differences in terms of the proportion of women who were foreign born. Most notably, almost a quarter of the non–drug-using women were foreign born.

More than a third of all the women were raised solely by their mothers. This was particularly the case for the drug-using women. About three fifths of women in both groups had not graduated from high school, and more than two thirds had never married. Only a few women in both groups were married to their infant's father.

A substantially higher proportion of drug-using women were homeless (29%), whereas (not shown in table) slightly more than a third of the non–drug-using women lived in institutions or with foster care families. A sixth of this last group were teenagers who were themselves dependents of the Juvenile Court of Los Angeles County.

Almost half of the drug-using women received support from Aid to Families with Dependent Children (AFDC) compared with about a fourth of the other women. Less than 5% of the entire sample of women were employed, either part-time or full-time, and virtually all of the women (97%) reported incomes under $5,000 per year.

Prenatal History, Mental Health, and Behaviors

As shown in Table 2, the percentage of women with a history of any prenatal care before the birth of the study infant was lower among the drug-using women (38%) than among the non–drug-using women (67%). Prenatal care was noted as received or not received; more detailed information about the number and timing of prenatal care visits was generally not recorded.

Almost a third of the non–drug-using women had mental health problems, such as schizophrenia, manic-depressive disorders, and affective disorders, compared with a much lower rate among the drug-using women (12%).

Mental retardation was recorded for 11% of the non–drug-using women and only 1.6% of the drug-using

TABLE 2.—*Prenatal Care History, Mental Health Status, and Behaviors of Drug-Using and Non–Drug-Using Women Whose Infants Were Referred to the Juvenile Court of Los Angeles County at Birth Before Hospital Discharge*

Women's Chorocterisitcs	Drug-Using Women (n = 1,155) (No.)* %	Non–Drug-Using Women (n = 236) (No.)* %	Totol (n = 1,391) (No.)* %
History of prenatal care†	(901) 38.0	(129) 66.7	(1,030) 41.6
Mental health problem†.	12.1	30.9	15.3
Mental retardation	1.6	11.0	3.2
Interaction with justice system			
Jailed at least once†	30.1	6.4	26.1
Multiple arrests†	(991) 37.4	(220) 10.0	(1,211) 32.5
Sexual history			
Multiple partners†	(1,004) 76.9	(190) 42.6	(1,194) 71.4
Prostitution	(1,136) 19.0	1.7	(1,149) 16.1

*Numbers are presented for variables with missing data.
†Group difference is significant at the .001 level using 2-tailed χ^2 tests.

women. Reasons for the court's removal of infants from the non–drug-using women (not shown in Table 2) included either recent or past evidence of either or both physical and sexual abuse of the infant's siblings (23%) and severe or general neglect (9%).

About a third of the drug-using women had been in jail at least once compared with less than a tenth of the other women. The drug-using women were also more likely to have a history of multiple arrests. As shown in Table 2, more than three quarters of the drug-using and slightly less than half of the non–drug-using women had a history of having multiple sex partners. Only a few non–drug-using women had been arrested for prostitution compared with a fifth of the drug-using women.

Two thirds of the drug-using women had never been enrolled in a drug rehabilitation program; nearly 5% of the women had been enrolled, but had dropped out (not shown). The drugs most commonly used by these women (not shown) were stimulants (cocaine, 87%; and methamphetamines, 7%), partial hallucinogens (marijuana, 28%; and phencyclidine piperdine [PCP], 9%), and heroin and other opiates (heroin, 12%; codeine, 3%; methadone, 3%; and other opiates, 4%). Most of their infants (89%) listed positive for one or more of these drugs; 94% of their infants either listed positive for drugs or showed signs of drug withdrawal at birth.

Childbearing Histories

Figure 1 compares the proportion of children of the drug-using women who were under court jurisdiction or DCFS supervision by family size. Overall, 3,124 (80%) of all of the 3,881 children born to these women were under the jurisdiction or supervision of the court. Although not shown in the figure, 80% of the children of the non–drug-using women were also under the jurisdiction or supervision of the court.

Additional Pregnancies

The DCFS records for 926 drug-using women who were observed for 18 months after the birth of the study infant revealed that 207 women (22%) had borne another infant in that period. Of these 207 infants, more than half (n = 111) had a positive drug immunoassay screen at birth and 123 (59%) were under the court's jurisdiction.

Of the 185 non–drug-using women with 18 months' follow-up, 14 (8%) had borne another child. None of these babies tested positive for drugs at birth. Nevertheless, 7 infants (50%) were placed under the court's jurisdiction.

Discussion

The drug-using women in this study were more likely than other women in the DCFS sample to be African American, raised by their mothers only, and homeless. They were also more likely to have been in jail, to have criminal histories and multiple sexual partners, and to have engaged in prostitution. The non–drug-using women were younger, less likely to be high school graduates, and less likely to be on AFDC, reflecting either their high rate of mental health problems or the fact that they were teenagers, nearly half of whom were also dependents under court jurisdiction. The non–drug-using women were also more likely to be mentally retarded and to have received some prenatal care. The last finding probably results from the supervision these women received, either from institutions or their foster care families.

More than half of the women in this sample were African American, and a fifth were Latina. How does the ethnic distribution of all women of childbearing age living in poverty in Los Angeles compare with these data? According to the 1990 census for Los Angeles County, among women aged 17 to 40 years living below the poverty level, 54.8% were Latina, 20.7% were white, and 14.2% were African American.[52] Thus, impoverished African-American women were significantly overrepresented in the DCFS samples, 59.8% versus 14.2%, whereas Latinas were significantly underrepresented, 21.9% versus 54.8%; whites were approximately equally represented.

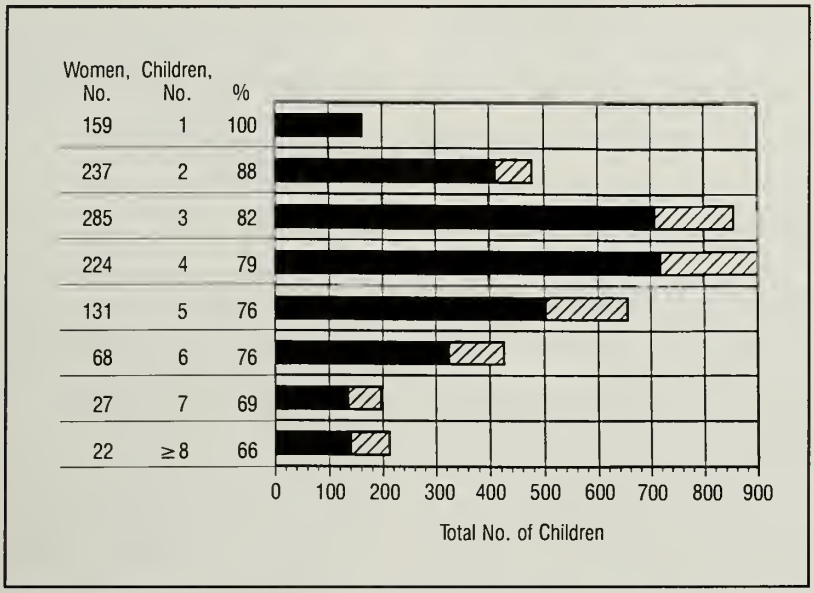

Figure 1.—The graph shows the number of children of drug-using women and the percentage of their children under the jurisdiction or supervision (or both) of the Juvenile Court of Los Angeles County, California. ■ = children of drug-using women under court jurisdiction or supervision or both; ▨ = children of drug-using women not under court jurisdiction or supervision.

A limitation of this study is that the predominance of African Americans in the sample of drug-using women may, in part, reflect ascertainment bias as reported by others[53,54] and by Los Angeles County hospital personnel because no monitoring process exists to ensure compliance with the law to assess parental competence to provide suitable care for infants suspected of prenatal drug exposure. A second limitation is that hospital personnel's knowledge of the placement of the women's other children under court custody may have predisposed them to screen their newborns for toxic substances. This form of ascertainment bias may, in fact, artificially elevate the study's main finding of a high percentage of the women's other children living in foster care. In other words, if a woman was not detected in previous pregnancies and her children not placed in foster care, she would be less likely to be detected during a subsequent pregnancy.

The cohort of drug-using women in this study, identified through the reporting of an index infant to DCFS and the court during the time interval specified, is a unique one. Although it does not represent all, or even some, well-defined proportion of the drug-using women in Los Angeles who bore an infant exposed to street drugs in utero during the time of this study, it does represent the new type of family requiring newborn foster care placement. In New York City, maternal cocaine use is the leading reason for infants being removed from their mothers at birth.[46] Some data suggest that as many as 80% of infants with prenatal drug exposure will be placed in foster care during their first year of life.[47] The lack of sufficient resources for the child welfare system to provide intensive services for the growing number of families who, before the cocaine epidemic, were maintained with less attention has been noted as a major crisis.[47]

About 400,000 children in the nation live in some type of foster care,[55] despite the fact that the demand for high-quality foster care outweighs the number of family placements available.[47,55,56] Not only is foster care itself expensive (in Los Angeles, the 1993-1994 budget for DCFS was just under $700 million), but foster care children also have higher rates of mental health, behavioral, and school problems[57-59] and physical health problems.[60] Clearly, the childbearing histories and major characteristics of drug-using and other poor women whose children become dependents of the Juvenile Court deserve serious investigation and action. The data from this study confirm those of others that show that the foster care population is increasingly one of drug-using and adolescent minority women and their children.[61] The lack of preventive, health, and social services and the subsequent consequences for mothers, their children, and the child health and welfare systems in the nation's second largest city cannot be ignored if, indeed, Los Angeles's reputation for forecasting to the nation holds true.

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Articles

Drug-Resistant *Mycobacterium tuberculosis* in California, 1991 to 1992

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To determine the proportion and distribution of drug-resistant *Mycobacterium tuberculosis* in California, we surveyed all California counties for drug-susceptibility test results for initial isolates from tuberculosis cases counted during the first quarters of 1991 and 1992. Overall, drug-susceptibility test results were not available for 17% of isolates. Among isolates with available test results, the proportion with resistance to isoniazid averaged 8.7%, and the proportion with resistance to at least 2 drugs, multidrug resistance, averaged 5.9% during these two quarters. The proportion of isolates with drug resistance did not change substantially during these time periods. The proportion with combined isoniazid and rifampin resistance remained stable at about 1.1%. Among persons whose isolates were tested for drug resistance, those with a known previous diagnosis of tuberculosis (relative risk [RR] = 2.6; 95% confidence interval [CI], 1.6 to 4.3; $P < .01$) and persons who were foreign born (RR = 1.7; 95% CI, 1.1 to 2.7; $P = .014$) were more likely to have isoniazid-resistant organisms. These statewide data suggest that the initial tuberculosis treatment regimen in California should include 4 antituberculosis drugs, as recommended by the American Thoracic Society and the Centers for Disease Control and Prevention for areas with a prevalence of isoniazid resistance of 4% or greater. The lack of test results for 1 in 6 patients with tuberculosis suggests the need for improved physician and laboratorian education to implement the recommendations that drug susceptibility be tested on all initial isolates.

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During 1975 to 1982, the Centers for Disease Control (now the Centers for Disease Control and Prevention; CDC) conducted surveillance for primary drug resistance among patients with tuberculosis (TB).[1-3] These surveys documented a 6.9% prevalence of resistance to one or more antituberculous drugs among isolates from 20 city and state laboratories across the nation (9.7% and 8.2%, respectively, from Los Angeles and San Francisco, California). From 1982 to 1986, the CDC also counted cases of TB with acquired (secondary) drug resistance.[4] The CDC stopped surveying for drug-resistant *Mycobacterium tuberculosis* in 1986 because of resource limitations and the decreasing trend of primary drug resistance.

In 1991, because of concern over the increasing incidence of TB and the outbreaks of multidrug-resistant TB, the CDC initiated a nationwide retrospective survey of drug susceptibilities of *M tuberculosis* organisms identified in cases counted during the first quarter of that year. Because drug-susceptibility test results were not routinely reported, the only source of statewide information about drug susceptibilities has been the first-quarter survey conducted by the CDC during 1991. We therefore repeated the first-quarter survey for 1992. Until ongoing surveillance is in place, these first-quarter surveys provide information regarding the magnitude of the problem in California that can be used to guide the choice of initial treatment regimens.

Patients and Methods

The study population consisted of all persons with cases of culture-positive tuberculosis counted in California during the first quarters of 1991 and 1992. A case of TB is counted by a county once the diagnosis has been confirmed. We sent each county a list of culture-positive cases counted within their jurisdiction for these two time periods. The information requested included whether drug susceptibility testing was done, when the first isolate was obtained, and drugs to which the isolate was resistant. On the questionnaire, we defined drug resistance as growth on a drug-containing medium (at any concentration tested) that is greater than 1% of that on the control medium.[5] We merged these data with the state Report of Verified Case of TB database to descriptively analyze drug-resistance patterns in California.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ATS = American Thoracic Society
CDC = Centers for Disease Control and Prevention
TB = tuberculosis

We calculated drug resistance based on the results of drug-susceptibility testing for isolates tested against that drug or a combination of drugs. For example, the denominator for the fraction of organisms resistant to isoniazid and rifampin includes only those tested against both isoniazid and rifampin. We defined multidrug resistance as resistance to two or more drugs.

We evaluated the proportion of isolates without drug-susceptibility test results and possible patient risk factors for not having such testing done, including age, sex, race, ethnicity, country of birth, previous treatment of TB, site of disease (primary or secondary pulmonary disease versus no pulmonary involvement), known diagnosis of the acquired immunodeficiency syndrome (AIDS) (status provided without personal identifiers by the state AIDS office), and vital state at the time of the diagnosis of TB. We examined these same patient risk factors and the possible association with an organism with drug resistance. We also compared the demographic and clinical characteristics of persons with culture-positive TB counted during the first quarters of 1991 and 1992 with those counted during the rest of those years.

We calculated relative risks and 95% Cornfield confidence intervals using Epi Info, version 5, software from the CDC.[6] We used Yates-corrected χ^2 and P values to test for significance.

Results

Of the 1,333 persons with culture-positive tuberculosis during the first quarters of 1991 and 1992, 220 (17%) did not have drug-susceptibility testing done on their initial isolates. Those who had died at the time of being diagnosed with TB were 2.1 times more likely than living patients not to have drug-susceptibility testing done. Women were 1.4 times more likely than men and non-Latinos were 1.3 times more likely than Latinos not to have drug susceptibility testing done on their *M tuberculosis* organisms (Table 1). Drug-susceptibility testing was done with similar frequency across all other racial or ethnic and age groups (data not shown). Being born in the United States, having a previous diagnosis of TB or a known diagnosis of AIDS, or having pulmonary disease did not influence the likelihood of having drug-susceptibility testing.

The proportion of organisms with isoniazid resistance averaged 8.7%, whereas the proportion with multidrug resistance averaged 5.9%. The proportion of organisms with resistance to any single drug, especially to isoniazid, to one or more drugs, to two or more drugs, and to both isoniazid and rifampin did not change significantly in California between the first quarters of 1991 and 1992 (Tables 2 and 3). The proportion of isolates with combined isoniazid and rifampin resistance remained constant at approximately 1.1%. Los Angeles, Orange, and San Francisco counties counted the largest number of cases of *M tuberculosis* isolates with resistance to isoniazid during these time periods, with 43, 14, and 9 cases, respectively, accounting for 9%, 13%, and 6% of isolates tested in those counties, respectively.

The resistance patterns did not change substantially during these two years, nor did the proportion of patients with risk factors for having a resistant organism; therefore, we combined the data from both years. Our analysis of risk factors associated with any drug resistance yielded results similar to those for isoniazid resistance. Given the American Thoracic Society (ATS) and the CDC's emphasis on the prevalence of isoniazid resistance as a basis for decisions regarding initial drug regimens,[7,8] we report comparisons only for isoniazid resistance.

Among persons whose organisms were tested for isoniazid resistance (Table 4), those with a known previous diagnosis of TB were nearly three times more likely to have an isoniazid-resistant organism than were persons with a first-time diagnosis of TB. Those who were foreign born were 1.7 times more likely than persons born in the

TABLE 1.—*Evaluation of Factors Associated With Not Having Drug Susceptibility Testing of* Mycobacterium tuberculosis *(TB) Organisms Performed, First Quarter Surveys, California 1991-1992*

Category	Isolates		RR (95% CI)	P Value
	No.	No. Not Tested (%)		
Deceased at diagnosis	57	19 (33)	2.1 (1.4-3.1)	<.001
Alive at diagnosis	1,274	200 (16)		
Women	467	92 (20)	1.4 (1.1-1.7)	.03
Men	866	128 (15)		
Non-Latino	876	157 (18)	1.3 (1.0-1.7)	.06
Latino	457	63 (14)		
US born	538	98 (18)	1.2	NS
Foreign born	778	119 (15)		
No previous diagnosis	1,239	205 (17)	1.1	NS
Previous TB diagnosis	91	14 (15)		

CI = confidence interval, NS = not significant, RR = relative risk

TABLE 2.—*Results of Drug-Susceptibility Testing of* Mycobacterium tuberculosis *Isolates for First-Line Drugs, First Quarter Surveys—California, 1991-1992*

Test	Year	M tuberculosis *Isolates* No. Tested	M tuberculosis *Isolates* No. Resistant (%)
Isoniazid	1991	602	48 (8.0)
	1992	508	49 (9.6)
Rifampin	1991	599	8 (1.3)
	1992	507	7 (1.4)
Streptomycin	1991	526	41 (7.8)
	1992	450	31 (6.9)
Pyrazinamide	1991	128	5 (3.9)
	1992	120	2 (1.7)
Ethambutol	1991	594	13 (2.2)
	1992	500	8 (1.6)

United States to have isoniazid-resistant TB. Controlling for birth on foreign soil yielded the same results for persons with a known previous TB diagnosis. Among those without a previous diagnosis of TB, foreign-born persons remained 1.8 times more likely to have an organism resistant to isoniazid ($P = .02$). Sex, ethnicity, patient's status at diagnosis, the site of disease, and having a known diagnosis of AIDS were not associated with isoniazid resistance. An analysis of risk factors for multidrug resistance yielded similar results (data not shown).

Differences in the proportion of isolates with resistance among racial or ethnic groups were not statistically significant. Asians and Pacific Islanders, however, were the racial or ethnic group with the highest proportion of isolates with isoniazid resistance. Of 349 *M tuberculosis* isolates from Asians and Pacific Islanders, 43 (12%) demonstrated resistance to isoniazid; all Asians and Pacific Islanders with resistant organisms were foreign born. Of 170 *M tuberculosis* isolates from African Americans, 16 (9%) were isoniazid-resistant, as were 28 of 393 *M tuberculosis* isolates (7%) from Latinos. Of 189 isolates from non-Latino whites, 10 (5%) were isoniazid-resistant. Only 1 (6%) of the 16 African Americans with isoniazid-resistant isolates was born outside the United States, and of 28 Latinos with isoniazid-resistant isolates, 22 (79%) were born outside this country. Among the foreign born, persons from Mexico, the Philippine Islands, and Vietnam accounted for the largest number of isoniazid-resistant organisms (Table 5). The number of years spent in the United States did not significantly influence the proportion of isolates with isoniazid resistance.

Isoniazid resistance was most prevalent among persons aged 15 to 24 (14/118, 12%) and 25 to 44 years (50/473, 11%). This relationship persisted even after the data were controlled for birth outside the United States or a previous diagnosis of TB. The proportion of isolates with isoniazid resistance was also greater than 4% among persons younger than 4 years, those 45 to 64 years, and those older than 65. None of the six isolates from persons aged 5 to 14 years was resistant to isoniazid.

Of the 12 persons with *M tuberculosis* organisms resistant to both isoniazid and rifampin, 8 (67%) were Asians or Pacific Islanders born outside the United States. Three (25%) were Latino, only one of whom was born outside the United States. Six (50%) had a previous diagnosis of tuberculosis. Of the 12 persons with isoniazid- and rifampin-resistant *M tuberculosis*, 11 (92%) had pulmonary disease, of whom 8 (73%) had both positive sputum smears and cultures, indicating possible infectiousness.

There were no significant differences among persons with culture-positive TB counted as cases during the first quarters of 1991 and 1992 and those counted during the rest of those two years with regard to age, sex, race, ethnicity, birth in the United States, and previous diagnosis of tuberculosis.

Discussion

With the resurgence of tuberculosis and the reported outbreaks of multidrug-resistant TB,[9-12] it is important for clinicians and public health officials to know the prevalence and the distribution of drug-resistant *M tuberculosis*. Multidrug resistance, especially combined isoniazid and rifampin resistance, can render the standard treatment regimen of isoniazid, rifampin, and pyrazinamide ineffective, complicating the choice of therapy. The recently released ATS and CDC guidelines recommend initial four-drug therapy for patients with TB in areas where the prevalence of isoniazid resistance is at least 4%.[7,8] The reasons cited for the recommended initial four-drug regimen include its effectiveness even against isoniazid-resistant organisms, more rapid sputum conversion to negative, an increased ease of administration once the switch is made to directly observed therapy, and an increased chance of cure even if therapy is incomplete. The CDC also recommends obtaining drug-susceptibility results on all initial *M tuberculosis* isolates to guide therapeutic decisions.[7]

Aside from the results of this study, there is little information about drug-susceptibility patterns in California. In one study, drug susceptibility was evaluated among patients admitted to a hospital in Los Angeles

TABLE 3.—*Overall Results of Drug-Susceptibility Testing for Culture-Positive* Mycobacterium tuberculosis, *First Quarter Surveys—California, 1991-1992**

Drug Resistance	Year	M tuberculosis *Isolates* No. Tested	M tuberculosis *Isolates* No. Resistant (%)
Resistant to ≥1 drug	1991	604	99 (15)
	1992	509	71 (15)
Resistant to ≥2 drugs	1991	603	33 (5.2)
	1992	507	32 (6.4)
Resistant to both isoniazid and rifampin	1991	599	6 (1.0)
	1992	507	6 (1.2)

*Drugs against which isolates may have been tested include first-line drugs as well as amikacin, ciprofloxacin, capreomycin, cycloserine, ethionamide, kanamycin, ofloxacin, aminosalicylic acid, and rifabutin.

TABLE 4.—*Evaluation of Risk Factors for Isoniazid Resistance, First Quarter Surveys—California, 1991-1992*

Category	Mycobacterium tuberculosis *Isolates*			
	No. Tested	*No. Resistant (%)*	*RR (95% CI)*	*P Value*
Previous TB diagnosis	77	16 (21)	2.6 (1.6-4.3)	<.001
No previous diagnosis	1,031	81 (8)		
Foreign born	657	70 (11)	1.7 (1.1-2.7)	.014
US born	439	27 (6)		
Men	736	60 (8)	.82	NS
Women	374	37 (10)		
Latino	393	28 (7)	.74	NS
Non-Latino	717	69 (10)		
Alive at diagnosis	1,071	97 (9)	*	NS
Deceased at diagnosis	38	0 (0)		

CI = confidence interval, NS = not significant, RR = relative risk, TB = tuberculosis

*Undefined.

County in the mid-1980s, and a prevalence of isoniazid resistance of 10% was found.[13] The most recent population-based study published from California was conducted in Santa Clara County from 1984 to 1986[14]; the authors reported that, among 256 isolates tested, 69 (27%) were resistant to one or more "first-line" drugs (isoniazid, rifampin, streptomycin, or ethambutol). Of these resistant organisms, 59 (86%) were identified in patients born outside the United States; only 44 (24%) of the 187 isolates without drug resistance were identified in foreign-born patients. Of the 256 isolates tested for drug susceptibilities, 31 (12%) were resistant to at least two drugs, and 6 (2.3%) were resistant to both isoniazid and rifampin.

Our study found that the proportion of *M tuberculosis* isolates with resistance to any drug in California, 15%, is comparable with the amount of resistance (14.2%) found during the nationwide first-quarter survey from 1991.[15] These data demonstrated no notable change in the pattern of drug resistance among *M tuberculosis* isolates tested in California between the first quarter of 1991 and that of 1992.

Consistent with the results of other studies, resistance to one or more antituberculosis drugs, especially to isoniazid, was more common among foreign-born persons and among those with a previous diagnosis of TB. These persons belong to population groups already known to be at risk for resistant TB, yet 15% of patients in each of these categories did not have testing for drug susceptibility done on their initial isolates. It is not clear why isoniazid resistance was more prevalent among persons aged 15 to 44 years.

The decreased frequency of susceptibility testing for persons who had died at the time of diagnosis suggests that physicians see less usefulness in doing drug testing for isolates from deceased patients. Drug-resistance information, however, is important for decisions regarding the clinical management of not only patients but also their contacts. Contacts of a person diagnosed with TB at death—that is, of a person who died without receiving antituberculous chemotherapy—are at greater risk of exposure because the health care professional would not have begun treatment of TB while the patient was alive.

Women and non-Latinos were less likely to have drug-susceptibility tests done on their *M tuberculosis* isolates. This finding suggests that physicians may be more aware of the risk of drug-resistant organisms among Latinos, although it is not clear why women would be less likely than men to have such testing done. Physicians should be reminded to obtain drug-susceptibility tests on initial *M tuberculosis* isolates from all patients, as recommended by the CDC.[7]

A possible limitation of the representativeness of these data is the year-to-year and quarter-to-quarter variation in case-counting practices; no uniform mechanism yet exists for ensuring systematic methods of case counting. The cases counted during the first quarters of 1991 and 1992 represent only 15% to 18% of the total number of cases reported to the state during these years. Two of the six counties reporting the largest number of TB cases during the first quarter of 1991, San Diego and Santa Clara counties, counted no cases during the first

TABLE 5.—*Proportion of* Mycobacterium tuberculosis *Isolates Resistant to Isoniazid, by Country of Origin for Foreign-Born Patients, First Quarter Surveys—California, 1991-1992*

Country of Origin	M tuberculosis *Organisms*		
	No. Tested	*No. Resistant*	*(%)*
Latin America			
Mexico	221	18	(8)
El Salvador	21	1	(5)
Guatemala	17	1	(6)
Other countries	35	2	(6)
Asia			
Philippines	107	10	(9)
Vietnam	80	15	(19)
China	55	9	(16)
South Korea	29	7	(17)
Laos	20	3	(15)
Other countries	43	2	(5)
Other countries or unknown	29	4	(14)

quarter of 1992, even though persons were diagnosed with TB during that period. The consistency of the results from each quarter imply that these data for drug-resistance patterns in California are reasonable preliminary estimates. Because information regarding only the first isolate was requested, these data give limited information about the incidence of acquired (secondary) drug resistance. The strong association between drug resistance and a previous diagnosis of TB suggests acquired drug resistance.

Another possible limitation of this study is that standard medical practice has not always included routine testing for drug susceptibilities. Our analysis was based only on those isolates tested, for which drug-susceptibility results were available. It is unclear what role clinicians' index of suspicion and the availability of testing or test results—including such issues as quality, timeliness, technologic advancement, and cost—may have played in causing an overestimate or an underestimate of the problem of drug resistance.

Despite accounting for a fifth of the nation's cases of TB (source: California Tuberculosis Control Branch) and despite reporting a proportion of foreign-born persons among patients with TB more than twice that of the rest of the country (60% versus 25%[15]), California seems to have a relatively low rate of multidrug-resistant TB, especially isoniazid- and rifampin-resistant TB, compared with the magnitude reported in New York[15,16] and possibly Florida.[9,10] There was a slight but not significant increase in the proportion of isoniazid-resistant isolates in California from 1991 to 1992, however. No racial or ethnic, age, or sex group had a proportion of isolates with isoniazid resistance of less than 4%, with the exception of those aged 5 to 14 years and American Indians (with fewer than 10 isolates tested from each group). Even among US-born patients and those without a previous diagnosis of TB, the proportion of isolates with isoniazid resistance was greater than 4%.

The results of this statewide analysis, therefore, suggest that all patients diagnosed with TB in California should be treated initially with the four-drug regimen as recommended by the ATS and the CDC,[7,8] unless local data define specific subgroups with a prevalence of isoniazid resistance of less than 4%. The four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol is preferred in California to the other recommended regimen of isoniazid, rifampin, pyrazinamide, and streptomycin because resistance to ethambutol was lower than that to streptomycin in this study. In addition, ethambutol is more readily available and can be taken orally, whereas streptomycin cannot. It should also be noted that resistance to both isoniazid and rifampin was only 1% during 1991 and 1992, suggesting that 99% of patients were susceptible to at least two of the drugs isoniazid, rifampin, and ethambutol and that the four-drug regimen that includes these drugs should be adequate for 99% of patients in California. The lack of drug-susceptibility testing for 17% of isolates shows the need for improved compliance with the CDC recommendation that drug-susceptibility testing be done on all initial isolates. Only then can the drug regimen be appropriately altered, if necessary.

The use of the expanded Report of Verified Case of TB, which began in January 1993, will allow state and local tuberculosis control programs and the CDC to monitor systematically both primary and acquired drug resistance among all new cases of TB. Health departments will also monitor the extent of physician compliance with the recommendations to do drug-susceptibility tests on all initial isolates and to first start with a four-drug regimen. These data, as well as information on the completion of therapy by patients, will allow a better definition of the causes of drug resistance and its trends so that control measures can be effectively directed.

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Articles

Varicella During Pregnancy
Maternal and Fetal Effects

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To determine the characteristics of maternal varicella at our institution, we reviewed all cases of primary varicella in pregnancy. Using a perinatal database that summarizes all obstetric admissions, we reviewed the medical records of women with varicella infections during pregnancy. Over a 5½-year period, 31 pregnancies were affected by varicella infection among 11,753 deliveries. The mean age of those patients was 19.6 years, significantly different from our overall population of 25.3 years ($P < .05$). The racial composition of 35% Hispanic, 35% white, and 29% African American was different from that of our general population of 55% white, 38% African American, and 6% Hispanic ($P = .023$). The mean gestational age of the eruption of vesicles was 25 weeks. Of the 31 women, 7 had preterm labor within a week of their varicella, 3 delivered prematurely, and 3 infants had a birth weight of less than 2,700 grams. Respiratory symptoms developed in 6 women, and pneumonia developed in 4, 2 of whom required ventilatory support, 1 for 5 days, the other for 49 days. Eight women received acyclovir during gestation, and none suffered sequelae. In all, 6 infants had lesions and anomalies noted at birth, 5 possibly associated with varicella.

Varicella infection is associated with a greater-than-expected level of both maternal and fetal morbidity. The fetal disease may occur due to maternal infection at any gestation and is most likely a spectrum of complications. The maternal disease appears to be worse in the latter half of pregnancy. Programs of prevention through vaccination must account for a possibly decreased level of immunity in different populations.

(Katz VL, Kuller JA, McMahon MJ, Warren MA, Wells SR: Varicella during pregnancy—Maternal and fetal effects. West J Med 1995; 163:446-450)

Varicella infection in pregnancy has possibly devastating consequences for both women and their fetus. The overall incidence of varicella in pregnancy has been estimated from 1 to 5 per 10,000.[1,2] Although it is a relatively benign disease in early childhood, the complications, both fetal and maternal, present several management problems for clinicians. Several issues regarding varicella in pregnancy are still debated, such as the spectrum and degree of fetal manifestations, the incidence and severity of varicella pneumonia, and the use of antiviral agents. Some authors have suggested that the rate of fetal manifestations is low if the maternal infection occurs more than a week from delivery, whereas others have reported a wide spectrum of fetal involvement.[3] The use of varicella-zoster immune globulin vaccine for chickenpox when maternal infection occurs within five days of delivery is an established practice, but the effectiveness of its use in preventing fetal disease is incomplete at best.[1,4] The use of acyclovir for the treatment of maternal chickenpox is also an area of discussion. Some investigators recommend treatment of any pregnant patient with varicella, but others recommend using the drug only for varicella pneumonia.[2,5-8] Data are incomplete as to the use and indications of antiviral agents. Recent admissions to our obstetric service of women with chickenpox and its subsequent morbidity led us to review the effects of this disease during pregnancy.

Patients and Methods

We reviewed the medical records for the period January 1989 through July 1994 of all patients admitted to the obstetric service at the University of North Carolina Hospital, Chapel Hill, both delivered and undelivered, who had chickenpox in pregnancy. All diagnoses were made clinically. The University Hospital is a tertiary-level referral center that cares for both a public and private population. It is the policy of the University Hospitals that all pregnant women be admitted to the obstetric service regardless of diagnosis. On discharge from the hospital, all obstetric patients' records are evaluated by a specially trained obstetric technician who records them in the perinatal database. All records are then reviewed by a senior perinatologist. Varicella is coded for specifically. Thus, if a woman had chickenpox

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in pregnancy, even if she was not admitted for that diagnosis, the event would be noted and her medical record could be retrieved.

Using a MEDLINE search with manual cross-reference, we reviewed recent literature regarding varicella, zoster, and chickenpox infections in pregnancy. Statistical analysis was performed with Fisher's exact test and *t* test with unequal variance. A *P* value of less than .05 was considered significant.

Results

From January 1989 through July 1994, there were 31 cases of pregnancy complicated by chickenpox infection on our obstetric service (Table 1). There were 32 live-born infants delivered (1 set of twins) and no cases of fetal demise. During this time period, 11,753 women were brought to delivery. Of the 31 women with chickenpox, 3 were referred from other institutions and 4 women delivered at other hospitals. The mean age of patients was 19.6 years ± 4.3 (1 standard deviation; range, 15 to 33 years).

Chickenpox developed in 11 women at 24 weeks or less. The mean date of delivery was 39 weeks (range, 35 to 42 weeks). Four women had delivery at less than 37 weeks. All four of these patients delivered within a week of the eruption of vesicles. Of the 32 infants, 3 had birth weights of less than 2,700 grams, and 3 infants had birth weights of less than the 10th percentile for their gestational ages. Two of the mothers of these three small-for-gestational-age infants had prenatal care starting late in their pregnancy: 19 and 27 weeks' gestation. The other had no specific risk factors for premature delivery. The smallest infant was 2,500 grams at 41-plus weeks. Three infants received acyclovir at birth for 14 days of therapy. The contacts for infection were documented in 10 of 31 patients, and all but 1 of the contacts were immediate family members.

Other than the preterm deliveries, five women had obstetric complications. There were three cases of preterm labor successfully managed with tocolysis. All three of the preterm labor episodes occurred within a week of the eruption of vesicles, and none of these women had histories of preterm labor. Thus, 7 of the 20 women (35%) who had infection after 24 weeks had preterm labor associated with their varicella. Although the rate of preterm labor in our population is 15.2%, we cannot compare the rates because of the referral nature of our population at a tertiary-care center. Another woman (3%) had third-trimester bleeding not related temporally to her chickenpox; 1% of our population has third-trimester bleeding. Preeclampsia developed in one woman, also distant from her varicella infection; 7% of our population is diagnosed with preeclampsia. We do not think that these last two complications were related to the varicella infections.

Of the 31 women, 6 had respiratory symptoms. Two women had dry coughs, symptoms of chest tightness, and mild tachypnea. They had no evidence of pneumonic involvement on chest x-ray films, and both had normal arterial blood gas measurements. One of the women was administered intravenous acyclovir for seven days, and the other was managed expectantly. Two other women had chest film findings suspicious for varicella pneumonia, in addition to having nonproductive coughs. Respiratory compromise did not develop in either of these patients, and after inpatient observation, both were discharged to home without sequelae. One of these women was treated for seven days with the administration of intravenous acyclovir. Severe varicella pneumonia developed in two patients, with morbid courses. The first, who was carrying a twin gestation at 23 weeks, had shortness of breath and tachypnea five days after the onset of her viral eruption. Intravenous acyclovir therapy was started, but her pulmonary status deteriorated and she required ventilatory support. She remained on a ventilator for five days and was an inpatient for 16 days. Her pulmonary recovery was unremarkable, and her twins were delivered at 38 weeks, appropriately grown and without evidence of congenital varicella.

TABLE 1.—*Demographic Characteristics of the Overall Obstetric Population Compared With Women With Varicella Infection, January 1989 to July 1994*

Demographics	Overall Obstetric Population, % (n=11,753)	Pregnant Women With Varicella Infection, %* (n=31)
Mean age, yr†	25.3 ± 6.2‡	19.6 ± 4.3
Ethnic association†		
Hispanic	6	35
White	53	35
African American	38	29
Parity		
Nulliparous	45	52

*Incidence, 2.6/1,000 pregnancies.
†$P < .05$.
‡Numbers are ±1 standard deviation.

The last patient, a 25-year-old gravida 3 para 1, had a varicella rash develop at 16 weeks of gestation. Her shortness of breath evolved 36 hours after the appearance of vesicles. The patient's respiratory status rapidly declined, and she was intubated four hours after admission. While receiving 100% oxygen before intubation, the patient's Po_2 was 70 mm of mercury, Pco_2 32 mm of mercury, pH 7.37, respiratory rate 48 breaths per minute, and saturation 94%. Treatment with intravenous acyclovir was begun, and a dopamine drip was initiated 24 hours later for decreased urine output. Secondary adult respiratory distress syndrome developed, requiring high ventilator settings. The patient continued to have a fraction of inspired oxygen of greater than 85% for four weeks. A tracheostomy was done at week 4. During the patient's second week on a respirator, staphylococcal sepsis developed, and in her fifth week in the hospital, *Pseudomonas aeruginosa* sepsis developed. Both were managed successfully with antibiotic therapy. She required 13 chest tubes for the treatment of persistent

and recurrent pneumothoraces. Parenteral nutrition was given from 18 to 25 weeks' gestation. The patient was gradually weaned off the ventilator and extubated on hospital day 49. The tracheostomy was capped on day 66. The patient was walking without oxygen by day 70. She gradually recovered as an outpatient, and at 37½ weeks, a 6-lb 8-oz male infant was delivered. Although the infant had no skin lesions or evidence of central nervous system involvement, he did have bilateral clubfeet.

Of the 31 women, 8 received acyclovir, and 2 other women received zoster immune globulin. One woman was given both. None of the 10 women had adverse reactions from these drugs. Of the 32 infants, 6 (19%) had anomalies. Two infants had skin lesions—old and new vesicles—at delivery, none with associated limb lesions or skin scarring. The maternal chickenpox in these cases occurred at 34 and 38 weeks' gestation, and one woman received zoster immune globulin during her infection. One infant (mentioned earlier) had bilateral clubfeet with maternal infection diagnosed at 16 weeks. One infant had meningomyelocele and hydrocephalus; maternal infection occurred at 25 weeks. One had a ventricular septal defect with a patent ductus arteriosus, necessitating neonatal digoxin therapy. This infant's mother had varicella at 20 weeks. The last infant had chronic respiratory difficulties for the first few months of life, characterized as a reactive airways syndrome. The mother of this infant had chickenpox at 24 weeks' gestation and was treated with acyclovir.

Discussion

Several major issues need consideration in cases of varicella in pregnancy: the effects of chickenpox on the pregnancy; the incidence and severity of varicella pneumonia; the treatment and prevention of varicella infection in pregnancy, particularly with acyclovir; and the effects of the infection on the fetus. These issues, although the subject of several reports and data sets, are still under discussion.

Our series and others in the literature indicate that chickenpox has a detrimental effect on pregnancy outcome. Seven women went into preterm labor within a week of their infection, although only four delivered premature infants. These women had varicella infections late in the third trimester. In another report of 43 women with varicella during pregnancy, 4 went into labor prematurely.[8] In a recent multicenter series of 106 pregnant women with varicella compared with age-matched controls, it was also found that the incidence of premature birth was substantially increased among women with chickenpox.[9]

Other authors have also reported cases of preterm labor and delivery associated with chickenpox.[6,10] The mechanism of the increased prevalence of preterm labor is unknown. It is tempting to speculate on the production of inflammatory mediators due to the viremia as being related to the preterm labor, given recent reports of the association of intrauterine cytokines and premature labor. We found at least one other report of a case of abruption in association with chickenpox.[4]

Several authors have suggested that either patients with chickenpox may have a greater predilection of pneumonia developing, or if pneumonia develops, it is more severe during pregnancy.[2,11-13] Others dispute this and feel there is not an increased incidence of pneumonia.[5] In our series, the incidence was 13% (4 of 31). Other authors report incidences of varicella pneumonia between 9% and 16%.[9,14,15] There are many reports of fatal varicella pneumonia occurring in all trimesters. It appears that pneumonia developing later in gestation, particularly in the third trimester, carries the highest mortality.[2,11,16] Of the four cases of varicella pneumonia in our series, the two patients requiring ventilation were in their second trimester. In 1968, 18 cases of varicella pneumonia in pregnancy were reported; it was this report that first noted the severe prognosis of varicella pneumonia in pregnancy.[14] In a review of 21 pregnancies complicated by varicella pneumonia, 12 women required ventilatory support, and 3 died.[2] In two reviews, one of 28 cases and another of 43, both described the need for ventilatory support; some cases were fatal.[8,11] In these and other reports, the authors suggested that there is an approximate maternal mortality of 40% with varicella pneumonia and recommended the use of intravenous acyclovir, suggesting that this may decrease maternal morbidity and mortality.[12] Although our data do not indicate whether pregnant women are at more risk for pneumonia developing, we agree with most authors that when pneumonia develops, it is more severe than in nonpregnant adults.

Nonvaricella pneumonia during pregnancy may also carry a higher morbidity and mortality compared with that in nonpregnant women.[17,18] The graver prognosis may be due to physiologic changes in immunity, altered pulmonary function, and fluid volume shifts during pregnancy. Many of the cases reported in the literature involve the development of the adult respiratory distress syndrome.

Most investigators concur that the use of intravenous acyclovir sodium, 10 to 15 mg per kg a day, is helpful in the management of varicella pneumonia. A higher dose of acyclovir is needed for varicella infection versus herpes simplex because the varicella virus is ten times less sensitive than herpes simplex to the effects of acyclovir.[15] Acyclovir inhibits viral DNA polymerase that is common to all the herpesviruses.[15,19] The major side effects from acyclovir are gastrointestinal upset, nausea, vomiting, and a potential for nephrotoxicity.[5,15,19] None of our patients, and few patients in the literature, have experienced difficulties with acyclovir.[6,20] Its safety is well documented for use in pregnancy, and it does not appear to be teratogenic. We support the position that in any pregnant patient with respiratory symptoms and chickenpox, treatment with acyclovir should be promptly started.

Currently, however, there is no published evidence that the use of acyclovir improves the outcome of

patients with uncomplicated chickenpox.[20] Chickenpox pneumonia is extremely contagious. Thus, when possible, our patients who were admitted to the hospital were put in negative-pressure rooms. Such rooms are certainly not easily available on obstetric wards and particularly in labor and delivery suites.

Our patient population appears fairly representative of that of the southeastern United States. Although 85% to 95% of adults in the United States are immune to varicella, the growing population of Hispanic women in the United States may create a larger proportion of patients susceptible to this disease.[9,11] This finding has public health implications. Other authors have suggested an increased susceptibility to varicella in adults from subtropical areas.[1] It is important that foreign-born persons residing in the United States, as well as recent immigrants, be included if varicella vaccination programs are to be effective.

Although the incidence of varicella in pregnancy has been estimated to be 1 to 5 per 10,000 women,[1,2] we are unsure why our incidence was approximately six times higher. Our higher incidence is only partially explained by referrals from other hospitals—3 of the 31 women. Larger, multi-institutional databases may better explain this finding.

The effects of varicella on the fetus is an area of concern.[9] The fetal involvement has been traditionally divided into three forms: "varicella embryopathy" stemming from maternal disease occurring before 20 weeks' gestation; congenital varicella resulting from maternal infection from 20 weeks' gestation until term, but more commonly close to term; and neonatal disease occurring when the pregnant patient has active lesions around the time of delivery. Varicella embryopathy was first described by Laforet and Lynch in 1947 and redefined by several authors since.[21-25] The embryopathy includes limb hypoplasia, skin scarring, central nervous system involvement, and other skeletal lesions.[22-25] Although it is most common before 20 weeks' gestation, the embryopathy has been reported from infection as late as 26 weeks.[3,26]

The largest series of congenital varicella was published recently.[27] In that report, 1,373 pregnancies from 1980 to 1993 in the United Kingdom and Germany were evaluated. The authors found that fetal disease occurred most commonly between 13 and 20 weeks. Fetal anomalies varied from skin lesions to lethal multiorgan system involvement. The use of zoster immune globulin in a pregnant woman may not eliminate the incidence of varicella embryopathy, but if given before maternal infection develops, it may decrease or attenuate fetal disease.[27] The incidence of embryopathy appears to be between 2% and 3%.[1,9,27] Investigators have emphasized that central nervous system involvement from the varicella may lead to deafness, cataracts, chorioretinitis, and microcephaly.[1,3,22]

If we define the embryopathy strictly as limb hypoplasia, skin scarring, and central nervous system lesions, there appears to be a low incidence of infection, less than 3%.[1,9,27] More likely the spectrum of viral manifestations is wider and merges with the syndrome referred to as congenital varicella. Congenital varicella may include skin, limb, and central nervous system effects, but also includes organ involvement such as blood, liver, and spleen.[1,3,22-24,27,28] It may manifest itself as a fulminant neonatal disease with maternal disease in the third trimester or with maternal infection remote from term.[3,24-25,27,28] In a recent review, it was emphasized that the wide spectrum of clinical manifestations in a neonate from maternal varicella included bowel obstruction, urinary tract anomalies, and microtia.[3]

Perhaps the most interesting aspect of congenital varicella is a theory advanced by Higa and co-workers.[28] These authors have postulated that the skin lesions, limb defects, and central nervous system lesions represent zoster infections in utero and that the fetal effects of varicella embryopathy are sequelae of repeated zoster infections in the fetus, including in utero encephalitis. This would explain many of the types of lesions and also the frequent appearance of active vesicles when children are born. Some infants with exposure to varicella during gestation will have no lesions at birth, but zoster will develop in the first two years of life, some will be born with skin scarring, and others will have active lesions.[3,27-29] This theory also explains why the embryopathy initially thought to occur before 20 weeks' gestation has been reported at much later gestations. The theory also links the specific anomalies seen with the embryopathy with the spectrum of lesions seen with the congenital varicella syndrome. Among our patients, it is unlikely that the lesion in the infant with an open neural tube defect was related to the mother's chickenpox. It is difficult to find an association between the varicella infection and the infant with reactive airways disease. Clubfeet and ventricular septal defects have been previously associated with maternal varicella infection,[3,27] but these lesions are common.

It is difficult to draw controls from our population because of the high referral rate of antepartum-diagnosed anomalies at our institution. Data from historical controls yield incidences of as much as 1.2 and 2.5 per 1,000 live births, respectively.[30] Similarly, hydrocephalus, meningocele, and patent ductus arteriosus are not uncommon. Without direct virologic evidence of varicella infection in the infants, we cannot say that there is a causal relationship between an anomaly and a maternal disease. Overall, in our series, 4 of 32 infants had lesions. We agree that pure varicella embryopathy is uncommon. We also concur with Higa and associates that fetal disease is a spectrum and that infection after 20 weeks' gestation is not always benign.

Congenital varicella has been diagnosed antenatally by ultrasound examination.[31] Cranial anomalies, polyhydramnios, hydrops, hyperechoic liver, hydronephrosis, and clubfeet have all been visualized sonographically. Prenatal diagnosis by umbilical blood sampling for immunoglobulin M and polymerase chain reaction for virus has also been reported.[32] It is important to note that

documented fetal infection does not necessarily mean there will be fetal defects.[8]

Many clinicians are under the impression that zoster immune globulin is effective for preventing chickenpox in infants. It is given to an infant when its mother has chickenpox within five days of delivery because there is not sufficient time for immunity to develop and to be transferred to the neonate. Varicella-zoster immune globulin in the dose of 125 U per 10 kg is only 50% effective in preventing the disease, although it may decrease overall severity.[1] There are many reports in the literature of chickenpox and congenital varicella, sometimes fatal, developing in infants despite the appropriate use of this immunizing agent.[1,4,33] Some authors have recommended increasing the dose to 250 U per 10 kg for neonates because of the numerous reported failures with 125 units.[34,35] Varicella-zoster immune globulin is not indicated for pregnant women after varicella lesions develop. Because of problems of obtaining titers in a timely way and the general immunity in the population, we do not routinely give this drug to a pregnant woman after exposure to chickenpox. If a pregnant woman has a known lack of immunity, however, its use would be an appropriate treatment after exposure. Varicella vaccine may be an important and worthwhile solution to the problems of this disease, but it should not be given during pregnancy.

Our series supports the findings of previous reviews that emphasize the severity of chickenpox in pregnancy, particularly the morbidity of varicella pneumonia. It also confirms the association of chickenpox with premature labor and delivery. The definition of varicella embryopathy may be too restrictive; congenital varicella may be a more appropriate term. Programs for preventing both maternal and fetal disease are the next logical step in our approach to varicella in pregnancy.

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Articles

Colorado Pediatricians' Involvement in Community Activities

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To determine Colorado American Academy of Pediatrics (AAP) pediatricians' involvement in community-based activities and awareness of and interest in the AAP Community Access to Child Health (CATCH) program, a 22-item survey was mailed to all general pediatrician AAP fellows and candidate fellows practicing in Colorado (n = 434). The return rate was 65%. Of the respondents, 73% provide direct patient care as their primary professional activity, 58% reported either current or past involvement in community-based programs outside of their practices, 91% of this community-based work was voluntary, and 80% of the respondents described this work as moderate to very rewarding. Half of the respondents (51%) were aware of the AAP CATCH program, and 68% were interested in attending a statewide CATCH meeting. We conclude that Colorado AAP pediatrician survey respondents participate heavily in community programs outside of their clinical practices and that among this group there is substantial interest in the AAP CATCH program.

(Brown J, Westrick MC, Rushton FE, Siegel C, LaMont R: Colorado pediatricians' involvement in community activities. West J Med 1995; 163:451-453)

Little has been published about physicians' involvement in community activities. What little that has been deals mostly with physicians' volunteer clinical work providing charity medical care or service in free medical clinics.[1-4] There are no articles available regarding the involvement of physicians in community-based activities outside of their practices such as in day-care facilities, Boys' and Girls' Club activities, church groups, community organizations, and recreation leagues. The goal of our study is to document Colorado State's American Academy of Pediatrics (AAP) pediatricians' involvement in their communities, both through and outside of their clinical practices, and to determine what impediments exist to becoming involved in community activities.

The goal of the AAP Community Access to Child Health (CATCH) program is to improve health care for children. This program, one of the AAP's community-based initiatives, was started so that pediatricians could work with other members of the community to solve children's health problems, often with local resources. Modeled after the successful "Healthy Children" program developed by Phil Porter, MD, in Boston, Massachusetts, and with support from the Robert Wood Johnson Foundation, CATCH seeks to effect change for children at the local level. The CATCH program has a pediatrician designated by each state AAP chapter as the state CATCH facilitator. These CATCH facilitators are available as consultants for local pediatricians with a desire to plan, finance, and implement a community-based project that addresses a specific community need. There are no data available to demonstrate pediatricians' knowledge of the CATCH program. An additional goal of our project is to determine the level of recognition by Colorado AAP pediatricians of the CATCH program and their willingness to become involved in CATCH activities.

Methods

All general pediatricians in Colorado who were identified as either fellows or candidate fellows of the AAP (n = 434) were mailed a 22-item survey. The survey included questions about the pediatrician's type of practice, diversity of patients served, extent and scope of community involvement, and any impediments to community involvement. In addition, pediatricians were asked about any unmet health- and non–health-related needs of children in their communities. Finally, the survey asked questions about the pediatrician's knowledge of the CATCH program and any interest they had in a statewide CATCH meeting. Nonresponders to the initial

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No reprints available.

ABBREVIATIONS USED IN TEXT

AAP = American Academy of Pediatrics
CATCH = Community Access to Child Health

survey mailing were sent a second survey questionnaire and encouraged to respond.

The survey responses were entered into a computer database (Paradox 3.5) using an IBM PC. Simple percentages of the respondents' answers to the survey questions were calculated using the database program and the spreadsheet Quattro Pro 3.0.

Results

Out of 434 surveys sent, 282 were returned, for a return rate of 65.0%. For this study, "respondent" refers to Colorado AAP pediatrician survey respondents. Percentages are calculated from individual question respondents rather than total survey respondents.

The respondents were to a great extent involved in primary care and for the most part worked in either a group or hospital setting (Table 1). A total of 58.0% of the respondents were either currently involved in community-based programs or had been involved in the past (Table 2). The type of involvement for this total group varied greatly, ranging from 17.7% in a clinic for poor or uninsured children to 14.3% in school health programs to 19.6% in various other types of programs, including church groups, various camps, and Head Start. The respondents initially got involved in these programs in a variety of ways (Table 2). A quarter (25.5%) began through a nonclinical community organization, 24.2% through their clinical practice, and 19.9% through the school system, among other ways. Of those involved, 91.2% worked with community-based programs at least partially on a voluntary basis, and a majority of the respondents involved spent at least three to five hours per month with their community group. Four fifths (80.0%) of the respondents found their involvement at least moderately rewarding.

TABLE 1.—*Characteristics of Respondents to Colorado CATCH Survey (n = 282)*

Chorocteristic	Respondents, %	Respondents, No.
Primary professional activity		
Direct patient care	73.1	209
Medical teaching	8.4	24
Resident or fellow	7.0	20
Clinical administration or management	4.9	14
Research	3.2	9
Public health administration or management	1.1	3
Retired	0.7	2
Other	1.8	5
Primary professional setting		
Group	28.5	79
Hospital	25.3	70
Solo or 2-physician practice	17.0	47
HMO	11.2	31
Medical school	8.7	24
Public clinic	5.1	14
Administrative office	1.1	3
Other	3.3	9

CATCH = Community Access to Child Health, HMO = health maintenance organization

TABLE 2.—*Colorado AAP Pediatricians' Reported Involvement in Community-Based Activities*

Community-Bosed Activity	Respondents, %	Respondents, No.
Currently participate in any community-based programs	51.6	143
No current participation but past participation in any community-based programs	6.4	18
Types of community programs with which currently involved		
Clinic for poor or uninsured children	17.7	57
School health program	14.3	46
Recreation program or sports team	12.4	40
Board of community organization	11.5	37
Boy or Girl Scouts	7.1	23
International health work	6.8	22
Day care	4.0	13
Homeless shelter	3.7	12
YMCA, Boys' and Girls' Club	2.8	9
Other	19.6	63
Voluntary community-based program participation	91.2	145
How they got involved in a community-based program		
Nonclinical community organization	25.5	59
Clinical practice	24.2	56
School system	19.9	46
Church activities	9.1	21
AAP, Colorado or national	3.9	9
Other	17.3	40
Level of reward to community participants		
Very rewarding	52.0	78
Moderately rewarding	28.0	42
Somewhat rewarding	17.3	26
Moderately or very unrewarding	2.7	4

AAP = American Academy of Pediatrics, YMCA = Young Men's Christian Association

Of those respondents who listed impediments to becoming involved in community-based programs in the future, most cited a lack of time as the primary reason. Others indicated that family obligations (children and spouses) were a large factor, whereas some respondents mentioned that they were unaware of the opportunities available.

Of all respondents, 87.6% reported unmet health needs for children in their community. These needs included immunization services, access to preventive medicine services, and access to primary health care, among others. Of all respondents, 83.5% reported unmet non–health-related needs for children in their community. These ranged from day care to school-based programs to recreational programs.

In regard to the respondents' awareness of the CATCH program, 50.8% reported that they were aware of it. Of all respondents, 67.6% reported a willingness to participate in a statewide CATCH meeting and 50.6% chose to coordinate such a meeting with the state AAP meeting.

Discussion

Most of the Colorado AAP pediatricians responding to our survey (58%) reported either current or past participation in community-based activities outside of their clinical practices. These community volunteers were mostly practicing clinicians, and they offered their time to a wide array of programs and activities, ranging from clinics for indigent children to recreational programs. In our opinion, the three to five hours per month spent by most of the respondents involved in these community-based programs is a generous amount. Most of the physicians participating in community-based programs (80%) found their work to be at least moderately rewarding. Few of those involved in their community had heard about community-based opportunities through the AAP. This indicates that the state AAP chapter could play a role in advertising and promoting available community volunteer work for interested pediatricians.

The AAP CATCH program is becoming widely recognized. Half of the respondents to our survey were aware of CATCH, and two thirds expressed interest in participating in a statewide CATCH meeting. The CATCH program is promulgated on the premise that pediatricians now and in the future are willing to become involved in their communities to improve access to health care for children. Nearly every chapter of the AAP has a pediatrician appointed as a facilitator to serve as a resource and convener for pediatricians who wish to work with parents, teachers, public health workers, social workers, public safety personnel, and others to develop systems to improve health care for children. The facilitators, assisted by personnel from the national AAP, hold chapter meetings for interested pediatricians to show what others have done to solve community problems, demonstrate what community resources are available for support, and provide information about the benefits of community pediatrics for children in local communities. The data in this report can serve as a valuable baseline for a later survey to determine if the CATCH program stimulated the involvement of more Colorado pediatricians (both in number and time commitment) in local community-based projects. Many pediatricians who responded to our survey are currently doing CATCH-like activities in their communities. A formal tie to the CATCH program may help them in their community-based programs and efforts.

The large unmet health- and non–health-related needs of children in the communities of most of the survey respondents suggest that few areas of the state—and probably the country—are immune to the problem of inadequate services for children. The wide range of types of services that are deficient in the communities of the survey respondents provides an insight into the magnitude of this problem.

Health care reform legislation continues to be widely debated and will clearly affect, both directly and indirectly, the availability and array of health services for infants, children, and adolescents throughout the United States. Regardless of the health care reform that does evolve, not all health and non-health needs of children will be met. In fact, the health care benefits packages that are developed for children may be far leaner than the comprehensive package many have advocated for. Pediatricians' voluntary involvement in community programs will undoubtedly continue to be an important supplementary form of services and care. In addition, organized programs like the AAP CATCH program will be valuable to assist pediatricians as they continue to participate on a local level with many other colleagues to fill the service gaps in their communities in meeting the needs of all children.

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Conferences and Reviews

Neuroendocrine Disorders of the Gut

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The regulation of gastrointestinal function is known to involve elements of the enteric nervous system. Processes such as secretion, motility, blood flow, and immune function are all influenced by a complex network of neurons whose cell bodies lie in the gut. These neurons use a wide spectrum of substances as neurotransmitters, although the majority use peptides once thought to function only as gut hormones. It has been increasingly recognized that abnormalities of this neuroendocrine regulatory system underlie many gastrointestinal disorders. The most obvious are states of peptide excess found in patients with gut endocrine tumors such as carcinoid, gastrinoma, and somatostatinoma. Conversely, other disorders appear to be related to deficiency states. Examples include both achalasia and Hirschsprung's disease (congenital megacolon), where the loss of inhibitory neural action leads to abnormalities of peristalsis and sphincter function. Evidence for abnormal neuroendocrine regulation leading to disease states is increasing for many other gastrointestinal disorders.

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At the turn of the century, gut function was thought to be regulated only by neural influences. This view was dramatically altered by an elegant series of experiments by W. M. Bayliss and E. H. Starling demonstrating the existence of a humoral factor that stimulated pancreatic secretion.[1] In dogs, acidification of denervated proximal jejunum or the intravenous administration of crude extracts of proximal jejunal mucosa markedly increased flow of pancreatic juices. These observations led to the conclusion that the jejunal mucosa contained a factor that was released into the bloodstream to circulate and stimulate the pancreas. They named this substance secretin. This was the first demonstration of hormonal action and marked the birth of endocrinology. Over the next 70 years, further evidence of endocrine control of gastrointestinal function was found in the actions of major peptides such as gastrin and cholecystokinin.

Since the 1970s, it has been increasingly recognized that many gastrointestinal peptides are found not only in endocrine cells, but also in neurons of the brain and the gut. Increasing evidence has recently supported the concept that these neuropeptides play important roles in the regulation of diverse gastrointestinal processes, including secretion, motility, blood flow, and immune function. Thus, today, both endocrine and neural regulation of gastrointestinal function is known to be important, both in normal digestion and in disease states. In this article, we review this "neuroendocrine" regulation of gut function and its related disorders.*

*See also the editorial by R. A. Liddle, MD, "Chemical Messengers of the Gut," on pages 485-486 of this issue.

Neuroendocrine Design of the Gut

Enteric Nervous System

The enteric nervous system (ENS) is defined as the system of neurons and supporting cells found in the gastrointestinal tract, including neurons of the pancreas and gallbladder.[2] The ENS is large, encompassing 80 to 100 million nerves within the gut. Embryologically, neurons of the ENS are derived from the neural crest. These neuroblasts migrate from proximal to distal in the gut during fetal life and develop interconnected neuronal networks or plexuses of great complexity. Two major types of plexuses are present in the intestinal tract: myenteric—consisting of neurons mainly responsible for controlling peristaltic activity; and submucosal—consisting of neurons mainly responsible for controlling secretion and absorption.

Individual enteric neurons can be grouped by function or histochemical properties. The following four functional classes of enteric neurons have been identified:

- Motoneurons—efferent or effector neurons that change the activity of the intestinal smooth muscle (such as muscle contraction, blood vessel dilation);
- Secretory neurons—efferent neurons regulating endocrine or exocrine secretion;
- Sensory neurons—afferent neurons carrying information such as wall tension of the intestine or the chemical nature of its contents to the central nervous system (CNS); and
- Interneurons—neurons that add structural complexity by forming information links between other enteric neurons.

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ABBREVIATIONS USED IN TEXT

APUD = amine precursor uptake and decarboxylation
CNS = central nervous system
ENS = enteric nervous system
VIP = vasoactive intestinal polypeptide

Motor and secretory neurons may be excitatory or inhibitory. Curiously, afferent neurons appear to outnumber efferent neurons in the ENS.

The substances used by enteric neurons as neurotransmitters have been identified histochemically. With this technique, five different types of neurons have been identified: cholinergic (acetylcholine), adrenergic (norepinephrine), serotoninergic (5-hydroxytryptamine), GABA-ergic (γ-aminobutyric acid), and peptidergic. Neurons containing nitric oxide synthase and using nitric oxide as a neurotransmitter have recently been identified in the gut.[3] These neurons may be separately classified as "nitrergic," but in many instances nitric oxide is co-localized with peptide neurotransmitters such as vasoactive intestinal polypeptide (VIP). Overall, peptidergic neurons are by far the largest group. Table 1 summarizes the peptides known to be present in enteric neurons.

TABLE 1.—*Neuropeptides of the Enteric Nervous System*

Vasoactive intestinal polypeptide
Peptide histidine isoleucine
Substance P
Substance K (neurokinin A)
Cholecystokinin
Somatostatin
Neuropeptide Y
Enkephalins
Dynorphin
Galanin
Calcitonin gene-related peptide
Gastrin-releasing peptide
Pituitary adenylate cyclase-activating polypeptide

Brain-Gut Axis

The ENS communicates with the CNS through both efferent and afferent pathways. This interaction has been called the brain-gut axis. Efferent CNS pathways, which may be either cholinergic or adrenergic, terminate at the level of ganglia within the gut. The release of neurotransmitters such as acetylcholine or norepinephrine activates postganglionic neurons of the ENS and influences gut function. Both efferent vagal parasympathetic and celiac sympathetic neurons function through this mechanism. Afferent pathways are composed of sensory fibers responding to stretch, noxious stimuli, and chemical changes. The stimulation of these fibers initiates the release of neurotransmitters such as substance P and calcitonin gene-related peptide, which activate local or long spinal reflexes. Extrinsic sensory neurons with cell bodies in the dorsal root ganglia allow such afferent communication from gastrointestinal tract ganglia to the CNS inferior vagal (nodose) ganglia. Many of the peptides found in enteric neurons are also present in the brain. For some peptides, such as cholecystokinin, brain concentration exceeds that of the gut. Administering these peptides to the CNS can alter gut function. In some instances, the central effect is opposite that of the peripheral effect.[4]

Gut Endocrine Cells

Endocrine cells of the gut are distinguished by their ability to produce peptide hormones from amine precursors. This *a*mine *p*recursor *u*ptake and *d*ecarboxylation led Pearse in 1966 to the APUD concept.[5] In this way, gut endocrine cells are similar to enteric neurons and cells of the hypothalamic-pituitary axis. These endocrine cells may be "open," with their apex exposed in the gut lumen, or "closed" within the organ. "Open" cells exposed to the lumen can be influenced by luminal stimuli, such as nutrients. "Closed" cells presumably detect luminal stimuli indirectly, through mechanisms that are poorly understood. The release of peptides from these cells may be into the bloodstream in classic endocrine action or into the interstitial fluid to act on nearby cells. This latter effect, called paracrine delivery, is likely an important regulatory mechanism in the gut for peptides such as somatostatin. Although endocrine cells of the gut were once thought to be derived from the

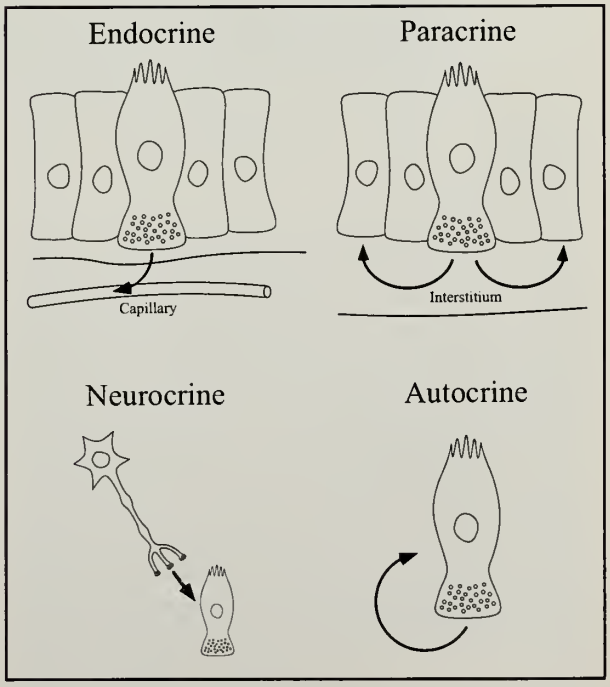

Figure 1.—The modes of the delivery of regulatory peptides to target cells are shown. In classic endocrine delivery, the hormone is secreted into the bloodstream, which carries it to the target cell. Paracrine delivery refers to the local diffusion of substances through interstitial fluid to target cells. Neurocrine delivery involves the release of substances by neurons innervating target cells. In autocrine delivery, cells release agents that affect their own function.

TABLE 2.—*Gastrointestinal Peptides and Their Major Actions*

Families of Peptides	*Major Actions*
Gastrin	
Gastrin	Stimulates gastric acid secretion
Cholecystokinin	Gallbladder contraction; pancreatic exocrine secretion
Secretin	
Secretin	Stimulates pancreatic fluid and bicarbonate secretion
Vasoactive intestinal polypeptide or peptide histidine isoleucine	Smooth muscle relaxation; intestinal secretion
Gastric inhibitory polypeptide	Enhances insulin release
Pituitary adenylate cyclase-activating polypeptide	Ileum or gallbladder contraction; pancreatic secretion
Pancreatic polypeptide	
Pancreatic polypeptide	Inhibits pancreatic exocrine secretion
Enteroglucagon	Enhances insulin release; stimulates mucosal growth
Peptide YY	Inhibits pancreatic secretion and acid secretion
Neuropeptide Y	Vasoconstriction; inhibition of pancreatic secretion
Tachykinin	
Substance P	Intestinal contraction; splanchnic vasodilation
Neurokinins A, B	Gut contraction
Opioid	
Neuromedin U	Gut contraction
Enkephalins	Gut motility inhibition
Dynorphin	Gut motility inhibition
β-Endorphin	Gut motility inhibition
Orphan	
Somatostatin	Inhibits release of other gastrointestinal peptides
Motilin	Sphincter contraction; associated with migratory motor complex
Neurotensin	Mesenteric vasodilation
Calcitonin gene-related peptide	Sensory neurotransmitter of gut reflexes
Gastrin-releasing peptide	Stimulates neural release of antral gastrin
Galanin	Inhibits insulin release; stimulates smooth muscle

neural crest, current evidence supports their endodermal origin.

Gastrointestinal Peptides

Gastrointestinal peptides are grouped into families, based on structural homology and mechanisms of release and action. Five identifiable families include those related to gastrin, secretin, pancreatic polypeptide, tachykinin, and opioids. A sixth group of gastrointestinal peptides with no known structural homology to others are called orphan peptides. These peptides, with their major actions, are listed in Table 2. Gastrointestinal peptides can be delivered to their target cells in one of four ways: endocrine, paracrine, neurocrine, or autocrine, as depicted in Figure 1. Gastrointestinal hormones, including secretin, gastrin, and cholecystokinin, are delivered to target cells in an endocrine manner through the bloodstream. Others, such as somatostatin, diffuse locally to their target in a paracrine manner. Neuropeptides, including gastrin-releasing peptide, substance P, and neuropeptide Y, are released from nerve endings and reach target cells by crossing a short synaptic gap. This is the dominant gastrointestinal peptide delivery method. Some peptides affect their own secretion, such as the inhibitory effect of somatostatin on its cell of origin, the D cell, and this is called autocrine delivery.

The release of gastrointestinal peptides is stimulated in many ways. Central effects, such as the sight, smell, and taste of food, stimulate the secretion of peptides such as gastrin by vagal efferent pathways. Peptide release is also mediated by the presence of food in the gut lumen. Examples include the stimulatory effect of amino acids on gastrin and cholecystokinin release. Other nutrients, such as fat, stimulate the release of cholecystokinin in the duodenum and peptide YY, neurotensin, and enteroglucagon from the ileum and colon. Other peptides are released in response to intraluminal pH. Examples include the release of somatostatin in response to antral acidification and secretin in response to duodenal acidification. Intestinal distention stimulates reflexes, causing the release of peptides affecting motility, such as VIP and substance P.

Gastrointestinal peptides act by binding and activating cell-surface receptors on target cells. The binding of a peptide with its receptor activates a cascade of intracellular events, resulting in the cellular response. Receptors and effectors may be part of the same molecule, or may be coupled through intermediary G proteins. Peptides such as VIP and secretin act through the second messenger, cyclic adenosine monophosphate, whereas cholecystokinin, gastrin, and acetylcholine act through diacylglycerol and intracellular calcium.

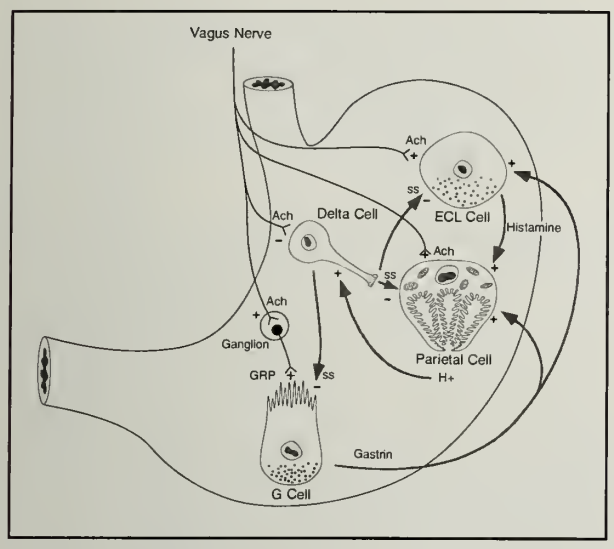

Figure 2.—The neuroendocrine control of gastric acid secretion is shown. Ach = acetylcholine, ECL = enterochromaffin-like, ss = somatostatin, GRP = gastrin-releasing peptide, + = stimulation, – = inhibition

Activation of these second messengers stimulates protein kinases and initiates cellular responses such as contraction, relaxation, and secretion.

Functions of the Enteric Nervous System

Regulation of Secretion

The ENS plays an important role in the regulation of both exocrine and endocrine secretion of the gut. These processes are best exemplified by the control of parietal cell function, a complex interplay of endocrine, neurocrine, and paracrine functions. At the thought, sight, smell, or taste of food, brain-stem vagal nuclei activate vagal efferent cholinergic fibers to stimulate postganglionic cholinergic neurons of the ENS within the gastric wall. The release of acetylcholine by these neurons stimulates parietal cell hydrogen ion secretion directly. Other cholinergic vagal efferent neurons stimulate enterochromaffin-like cells to release histamine that, in turn, stimulates parietal cell acid secretion through a paracrine pathway. Additional vagal efferent neurons stimulate the release of gastrin-releasing peptide from ENS neurons. Gastrin-releasing peptide stimulates antral G cells to release gastrin into the blood. Circulating gastrin potently stimulates the parietal cell directly by binding to parietal cell gastrin receptors and indirectly by stimulating enterochromaffin-like cell histamine release. Finally, central cholinergic stimulation also increases acid secretion through the inhibition of the release of somatostatin from gastric D cells. On emptying of a meal from the stomach, somatostatin provides feedback inhibition of further parietal cell acid secretion. Somatostatin is released in response to antral acidification and inhibits acid secretion indirectly by inhibiting G-cell gastrin release[6] and enterochromaffin-like cell histamine release and directly by inhibiting parietal cells.[7] These pathways are summarized in Figure 2. Other secretory processes regulated by the ENS include pancreatic exocrine secretion by gastropancreatic and enteropancreatic reflexes and intestinal and colonic secretion by neurons containing VIP.

Regulation of Motility

Gastrointestinal smooth muscle cells are controlled predominantly by the ENS, but are subject to additional endocrine and CNS influence. The three most important aspects of gastrointestinal motility are peristalsis, the migratory motor complex, and sphincter function.

Peristalsis is coordinated contraction and relaxation of the gut that results in the distal transit of a meal. This process is intrinsic to the gut and occurs even after extrinsic denervation. It is now known that peristalsis is regulated by the ENS. The mechanisms of ENS regulation of peristalsis have been determined largely from studies of isolated intestinal muscle strips. Stretch stimulation initiates a proximal contraction reflex that appears to be mediated by neurons using acetylcholine and substance P as neurotransmitters. Simultaneously, intestinal stretch induces a distal relaxation reflex, allowing the propagation of the meal. This reflex is mediated by neurons containing VIP and nitric oxide as neurotransmitters.[8,9]

The migratory motor complex refers to the strong propulsive wave observed at regular intervals in the fasted state that sweeps down the entire gut, clearing it of food particles. The migratory motor complex has been appropriately called the "housekeeper" of the gut and probably serves to prevent intestinal bacterial overgrowth, stasis, and malabsorption. The migratory motor complex originates from a gastric pacemaker on the proximal greater curvature and migrates distally down the gut in four recognizable phases. Although vagotomy and sympathectomy do not alter the complex, the ingestion of food abolishes it and returns the intestine to a fed pattern. The major propulsive wave occurs during phase III of the motor complex. This phase has been associated with a rise in serum motilin levels, but a cause-and-effect relationship has not been established.

The relaxation and contraction of the sphincters of the gut, including those of the lower esophagus, pylorus, ampulla of Vater, ileocecal valve, and internal anal sphincter, are regulated by the ENS. In general, nitric oxide and "VIPergic" neurons mediate relaxation, and either or both cholinergic and adrenergic neurons mediate the contraction of sphincters.

Neuroendocrine Disorders of the Gut

Better understanding of normal gut function has led to the clarification of the pathophysiology of some heretofore mysterious gastrointestinal disorders. The complex nature of the regulatory processes in the gut and the diffuse nature of the gut neuroendocrine system have made the study of these disorders difficult. In addi-

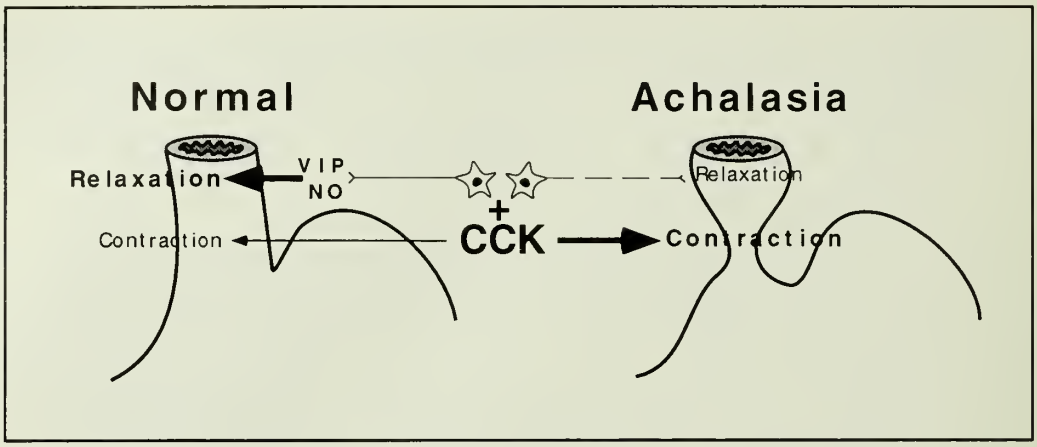

Figure 3.—The regulation of the lower esophageal sphincter (LES) by the enteric nervous system is shown. Relaxation of the LES is caused by inhibitory neurons using vasoactive intestinal polypeptide (**VIP**) and nitric oxide (**NO**) as neurotransmitters. Cholecystokinin (**CCK**) likely has a dual effect: directly contracting LES muscle fibers and indirectly relaxing the LES by stimulating VIP- and NO-containing neurons. In normal persons, the inhibitory mechanisms predominate. In patients with achalasia, the inhibitory neural reflexes are lost, resulting in a tonically contracted, high-pressure LES.

tion, unlike other endocrine organs such as the thyroid or adrenal gland, states of regulatory peptide excess or deficiency have not always been easily recognizable as diseases. Several disorders of gut function have now been attributed to abnormalities of neuroendocrine regulation. These disorders are summarized as follows.

Achalasia

Achalasia is an esophageal motility disorder characterized by abnormal or absent peristalsis in the body of the esophagus, a high-pressure lower esophageal sphincter, and failure of the lower esophageal sphincter to relax with deglutition. These functional abnormalities are due to defects in ENS regulation of esophageal motility, which is mainly due to a loss of inhibitory neurons. An impairment of inhibitory neuron function is demonstrated by the paradoxical increase in lower esophageal sphincter pressure observed in response to cholecystokinin in patients with achalasia.[10] Immunochemical studies reveal a decreased number of or absent VIPergic and nitrergic neurons in the lower esophagus and the lower esophageal sphincter in patients with achalasia.[11,12] The intravenous administration of VIP decreases lower esophageal sphincter pressure in patients with achalasia, but not normal persons, suggesting that in achalasia, the lower esophageal sphincter may be supersensitive to VIP.[13] Although lower esophageal sphincter pressure can sometimes be reduced with long-acting nitrates or calcium channel blockers, many patients require myotomy of the sphincter. Its regulation is summarized in Figure 3.

Chagas' Disease

Chagas' disease is caused by infestation with the parasite *Trypanosoma cruzi*. This parasite produces a neurotoxin that causes irreversible damage to submucosal and myenteric neural plexuses throughout the body. Gastrointestinal manifestations of this neuropathy include megaesophagus due to failure of the lower esophageal sphincter to relax and dilation of both the small bowel and colon due to the failure of peristalsis.

Gastric Dysrhythmias

Unexplained vomiting is occasionally found to be due to abnormal gastric electrical activity, referred to as gastric dysrhythmia. Several patterns of abnormal electrical activity have been identified. In some patients, an ectopic gastric pacemaker is present, leading to tachygastria.[14] This ectopic pacemaker disrupts phase III of the migratory motor complex, with uncoupling of fundic and antral coordination, resulting in poor antral grinding and delayed gastric emptying. An abnormal gastric electrical pattern has also been observed in patients with postoperative ileus, motion sickness, diabetic gastroparesis, and anorexia nervosa. Some of these patients benefit from promotility agents, including metoclopramide hydrochloride (a dopamine antagonist that acts as a cholinomimetic in the antrum), cisapride (which enhances acetylcholine release at peripheral gut sites), and erythromycin (an antibiotic that activates gut motilin receptors).

Hypertrophic Pyloric Stenosis

Pyloric stenosis is a congenital obstructing lesion found most commonly during the first six months of life. Histologic findings include pyloric muscle hypertrophy, mucosal edema, and submucosal lymphocytic infiltration, without notable anatomic changes in ganglia. Although its pathogenesis is unknown, defects in ENS regulation of the sphincter appear to play a role. For example, nitric oxide synthase is lacking in pyloric tissue from infants with pyloric stenosis.[15] In addition, in genetically altered mice lacking the neuronal nitric oxide synthase gene, a disorder resembling human pyloric stenosis develops, with grossly enlarged stomachs and hypertrophy of the pyloric musculature.[16]

Previous studies have suggested that abnormalities of other gut peptides may play a pathogenic role, as the administration of exogenous pentagastrin to pregnant dogs induces pyloric hypertrophy in some offspring.[17] Surgical pyloromyotomy remains the preferred treatment method.

Scleroderma

Scleroderma, a multisystem disorder characterized by obliterative vasculitis and the proliferation of connective tissue, can affect the gastrointestinal tract from the mouth to the anus. Gastrointestinal symptoms include pain, bloating, dysphagia, constipation, and malabsorption. Defects in esophageal motility, gastric emptying, and intestinal peristalsis have been identified. Electrical activity corresponding to phase III of the migratory motor complex is diminished in amplitude and frequency in patients with scleroderma, whereas serum motilin levels are elevated.[18] Administering the somatostatin analogue octreotide increases the frequency of the migratory motor complex and reduces malabsorption and symptoms in severely afflicted patients.[19] Although the mechanism of this effect is unclear, somatostatin is a neurotransmitter in myenteric neurons of the small and large intestine and stimulates myenteric acetylcholine release.[20]

Irritable Bowel Syndrome

The irritable bowel syndrome is a functional motor disorder characterized by alternating constipation and diarrhea and abdominal pain in the absence of detectable organic disease. Recent evidence suggests that this group of disorders may be caused by alterations in the regulation of gut motility by the ENS. Administering cholecystokinin increases colonic activity and abdominal pain in some patients with the irritable bowel syndrome, suggesting that meal-induced cholecystokinin release may account for postprandial pain.[21] In addition, an alteration in the sensitivity of gut afferent neurons, mediating the perception of pain, is thought to contribute to this syndrome. Patients with the irritable bowel syndrome have an increased perception of pain in response to sigmoid balloon dilation compared with control patients.[22] Heightened sensitivity of visceral afferent neurons to normal endogenous stimuli may play a role in other functional bowel diseases such as noncardiac chest pain and nonulcer dyspepsia.

Inflammatory Bowel Disease

The ENS plays a major role in modulating the gut immune response. Recent evidence suggests that alterations in the ENS are involved in the pathophysiology of inflammatory bowel disease. Neuropeptides such as substance P, VIP, enkephalin, and somatostatin alter lymphocyte function.[23] Conversely, cytokine products of the immune system have clear effects on gut function. In patients with Crohn's disease, the number of rectal VIPergic neurons is increased immunohistochemically, as are concentrations of rectal mucosa VIP.[24] Furthermore, the number of substance P receptors is increased in colon from patients with inflammatory bowel disease.[25] The expression of several recently described neuropeptides, the trefoil peptides, may also be found in patients with inflammatory bowel disease.[26] In addition to this evidence of abnormalities in gut peptides, other studies have identified increased circulating and mucosal cytokine production in patients with inflammatory bowel disease.[27,28] Thus, this disease may be related to alterations in immune-ENS interactions that result in inflammation and diarrhea. This area is currently the subject of intensive investigation.

Pseudo-obstruction

A few patients present with features of intestinal obstruction in the absence of any mechanical lesion. This so-called intestinal pseudo-obstruction has both acute and chronic forms. Both appear to be caused by abnormalities in the regulation of peristalsis by the ENS. Chronic intestinal pseudo-obstruction may be acquired, but it also has a familial form. Abnormalities of intestinal ganglia have been identified immunocytochemically in patients with chronic intestinal pseudo-obstruction.[29] No uniform pattern has been found, however, suggesting that this disorder may represent the clinical expression of any one of several regulatory defects. The administration of cisapride relieves symptoms in some patients with chronic pseudo-obstruction, but no therapy has proved uniformly beneficial.[30]

Chronic Constipation

Although the cause of chronic constipation is varied, some patients appear to have abnormalities in ENS regulation of colonic motility. Three patterns of abnormal motility have been identified: generalized aperistalsis, rectosigmoid junction dysmotility, and anal sphincter dysfunction.[31] Studies of patients with chronic constipation suggest that colonic VIP levels are decreased or absent and that serotonin levels are increased.[32,33]

Hirschsprung's Disease

Hirschsprung's disease is one of the most clearly documented disorders of gut function related to defects in the ENS. Afflicted patients present with colon obstruction in infancy or, more rarely, with chronic constipation in adulthood. This disorder is due to the absence of intramural ganglion cells in the colon and rectum. The aganglionic segment always involves the internal anal sphincter and has variable extension proximally. The congenital defect is thought to be due to an arrest in caudad migration of neuroblasts from the neural crest to the distal gut during development.[34] Histologically, abundant hyperplastic neurons are present in the gut wall, but ganglion cells are absent. The absence of relaxant enteric neurons and ganglia containing VIP and nitric oxide in the involved segments is thought to cause the pronounced colonic spasticity seen in patients with Hirschsprung's disease.[35-37] Other peptides, including substance P, may also have a role.[38]

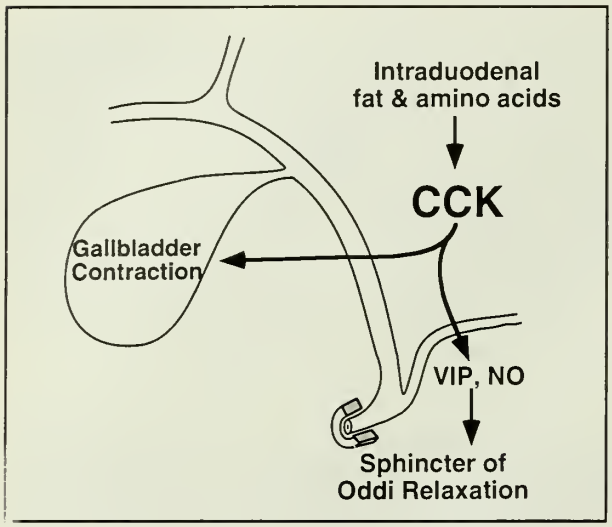

Figure 4.—The regulation of sphincter of Oddi function by the enteric nervous system is shown. With the ingestion of a meal, intraduodenal fat and amino acids cause the release of cholecystokinin (**CCK**) from duodenal endocrine cells. Cholecystokinin has a dual action, directly causing gallbladder contraction and simultaneously causing relaxation of Oddi's sphincter. This latter effect is indirect and mediated by the release of vasoactive intestinal polypeptide (**VIP**) and nitric oxide (**NO**) from inhibitory neurons innervating sphincter smooth muscle.

At present, resection of the involved colonic segment is the treatment of choice for patients with Hirschsprung's disease.

Sphincter of Oddi Dyskinesia

About 10% of patients undergoing evaluation of postcholecystectomy pain are found to have abnormal tonic or stimulated sphincter of Oddi motility. The regulation of function of Oddi's sphincter is under the control of neurons of the ENS. In humans, cholecystokinin contracts the gallbladder and decreases both basal tone and phasic wave activity in the sphincter. As shown in Figure 4, this last effect is indirect and mediated by VIP and nitric oxide release from inhibitory sphincter neurons. In some patients, the administration of exogenous cholecystokinin causes a paradoxical increase in sphincter tone concomitant with gallbladder contraction, resulting in pain.[39] This suggests a loss of inhibitory innervation akin to that observed in achalasia. Direct neural connections from the gallbladder to the sphincter mediating relaxation have been identified. It is possible that cholecystectomy, in some patients, may alter these reflex pathways.

Endocrine Tumors of the Gut

The rare examples of peptide excess states leading to disorders of gastrointestinal function are related to tumors that secrete gut peptides and amines. These tumors, although uncommon, have provided important insights into the physiologic effects of their secretory products. A summary of the major endocrine tumors of the gut is given in Table 3. Although a given tumor secretes a dominant peptide, leading to a clinically identifiable syndrome, many gut endocrine tumors release multiple peptide products. These lesser products (such as somatostatin) occasionally ameliorate the clinical symptoms. Radiolabeled peptides, octreotide and VIP, have recently been used successfully to localize these interesting tumors.[40,41]

Carcinoid Syndrome

Carcinoids are APUD tumors, and although they occur throughout the length of the gastrointestinal tract, 95% originate in one of three sites: the appendix, rectum, or ileum. Although the endocrine products of the primary tumor are metabolized by the liver, in the face of metastatic disease or bronchial or ovarian primary, they may circulate and cause the carcinoid syndrome, manifested mainly by flushing and diarrhea. Associated conditions include asthma, valvular heart disease, and pellagra. Carcinoid tumors release a number of peptide

TABLE 3.—*Major Endocrine Tumors of the Gut*

Tumor	*Cell Type*	*Clinical Features*
Carcinoid	Enterochromaffin or enterochromaffin-like	Cutaneous flushing, diarrhea
Gastrinoma	G cell, islet non-β cell	Peptic ulceration, diarrhea
Vipoma	Islet D_1 cell	Verner-Morrison or WDHA syndrome: watery diarrhea, hypokalemia, achlorhydria
Somatostatinoma	Islet D cell	Diabetes mellitus, steatorrhea, gallstones
Insulinoma	Islet β cell	Whipple's triad: low fasting blood glucose level (<2.5 mmol/liter), symptoms of hypoglycemia induced by fasting (such as trembling, weakness, mental confusion), and relief of symptoms by oral or intravenous glucose
Glucagonoma	Islet A cell	Mild diabetes, migratory necrolytic erythema, glossitis
PPoma	Islet PP cell	Usually clinically silent

products, including serotonin (5-hydroxytryptamine), substance P, histamine, kallikrein, and neurotensin. The metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), is found in the urine and is widely used as a tumor marker. The symptoms of the carcinoid syndrome are caused by the secretion of these vasoactive amines and peptides. The watery diarrhea, caused by rapid transit in the intestinal tract,[42] may be due to circulating serotonin, as this symptom can be abolished with the administration of serotonin antagonists. Bradykinin, neurotensin, and substance P appear responsible for flushing. Tumor substance release can be inhibited and symptoms palliated with the administration of octreotide. Selected patients benefit from cytotoxic chemotherapy or surgical resection.

Gastrinoma

In 1955, Zollinger and Ellison described a syndrome of severe peptic ulcer disease and gastric acid hypersecretion associated with non–β-islet cell tumors of the pancreas.[43] After the development of radioimmunoassay, it was proved that gastrin was the cause of this syndrome. Although they were initially described as pancreatic tumors, it has been increasingly evident that a substantial fraction of these tumors arise in extrapancreatic sites, particularly the duodenum. Peptic ulceration, which occurs in more than 90% of patients, is due to parietal cell stimulation by the potent secretagogue gastrin. Gastrin also causes a pronounced gastric epithelial hypertrophy. The diarrhea in gastrinoma is caused by the delivery of large volumes of acidic gastric contents to the small bowel and the stimulation of intestinal peristalsis by circulating gastrin. Increased luminal acid inactivates pancreatic lipase, resulting in steatorrhea. Although administering the hydrogen-potassium-adenosine triphosphatase inhibitor omeprazole effectively treats symptoms of gastrinoma by blocking parietal cell acid secretion, 50% of patients die of metastatic gastrinoma. Thus, surgical resection, when possible, is the optimal treatment of patients with these tumors.

Vipoma

Vipomas are rare neuroendocrine tumors that secrete excessive amounts of VIP. More than 80% are localized to the pancreas, and about 60% are malignant. The excess production of VIP by these tumors accounts for the clinical syndrome of *w*atery *d*iarrhea, *h*ypokalemia, and *a*chlorhydria (WDHA syndrome).[44] The excess VIP causes small intestinal and colonic secretion of bicarbonate- and potassium-rich fluid, leading to alkaline diarrhea, hypovolemia, hypokalemia, and metabolic acidosis. Vasoactive intestinal polypeptide also inhibits acid secretion, resulting in hypochlorhydria or achlorhydria. Diagnosis is made by identifying elevated plasma VIP levels associated with large-volume secretory diarrhea. The medical treatment of choice is the use of the somatostatin analogue octreotide, which controls diarrhea in more than 80% of patients.[45] Surgical excision should be considered in all patients without metastatic disease.

Somatostatinoma

Somatostatinomas are rare endocrine tumors usually found in the pancreas or duodenum. About 80% have metastasized by the time of diagnosis. These tumors produce and release large amounts of somatostatin. The elevated circulating somatostatin levels cause a distinct clinical syndrome of mild diabetes mellitus, gallstones, steatorrhea, and weight loss. The diabetes is caused by the inhibition of islet insulin release by somatostatin. The diabetes is usually mild, probably due to a concomitant inhibition of glucagon release. Gallstones likely result from the inhibition of gallbladder emptying by somatostatin. This effect may occur both by a direct inhibition of gallbladder motility and indirectly through the inhibition of cholecystokinin release. Steatorrhea is caused by the profound inhibition of pancreatic enzyme secretion by somatostatin. At present, surgical resection and chemotherapy are the main therapeutic options.

Other Gut Endocrine Tumors

The most common pancreatic islet cell tumor is insulinoma, but this tumor rarely causes gastrointestinal symptoms. Similarly, glucagonoma is virtually never found in extrapancreatic primary sites and rarely presents with gastrointestinal symptoms. Much more rarely encountered are tumors secreting pancreatic polypeptide ("PPoma"). These tumors usually arise in the head of the pancreas and are ordinarily clinically silent. Tumors have occasionally been reported to cause diarrhea or peptic ulceration, but it is possible that these effects are caused by peptide products of the tumors rather than pancreatic polypeptide itself.

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Unproven (Questionable) Cancer Therapies

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More than half of all cancer patients use some form of alternative treatment during the course of their illness. Alternative therapies are often started early in patients' illness, and their use is frequently not acknowledged to health care professionals. Some alternative therapies are harmful, and their promoters may be fraudulent. Persons who try alternative cancer therapies may not be poorly educated but may ultimately abandon conventional treatment. Recent attention has focused on aspects of questionable therapies that make these treatments attractive to patients and that may be perceived as being deficient in the practice of conventional health care professionals. Physicians with patients with cancer should always make sure that unproven therapies are discussed early in the therapeutic relationship. They should also attempt to be aware of alternative therapies that are in vogue in their particular geographic area.

(Brigden ML: Unproven [questionable] cancer therapies. West J Med 1995; 163:463-469)

During the next year, several hundred thousand Americans will be diagnosed with cancer. Of these new patients, more than 50% will participate in some form of "unproven" or "unorthodox" therapy.[1-3] About 40% of these patients with cancer will begin such therapy when they are free of symptoms or in the first stages of their disease.[3] In more than 70% of such cases, patients will not tell their physicians that they are using unconventional therapy.[4] Studies indicate that most patients tend to use questionable cancer therapies as adjunctive rather than primary therapies.[2] Other investigations have shown, however, that as much as 40% of patients who commence unorthodox therapy ultimately completely abandon conventional treatments.[1,3] "Unproven," "unorthodox," or "alternative" cancer treatments have been broadly defined as those therapies that have not been objectively, reliably, responsibly, and reproducibly demonstrated in peer-reviewed studies to be more effective than suggestion or doing nothing.[5] The demonstration of efficacy must be carried out in a way that separates cause and effect from coincidence, suggestibility, the natural history of the disorder, and pure fabrication. Simply because a treatment is unproven or alternative does not mean it is always of questionable value. But, according to the rules of science and law, proponents of new therapies bear the burden of scientifically validating their efficacy and safety. Simply claiming effectiveness on the basis of testimonials is not sufficient. On the few occasions that alternative treatments have actually been subjected to properly controlled scientific trials, they have been found wanting. For most questionable cancer treatments, no such trials have been carried out.[6-8]

Quackery is a lay term that is frequently applied to unproven treatments if they are given for profit.[9,10] This term originates from the German *quacksalver*, which means to quack like a duck about oneself or the virtues of one's therapies. A 1993 telephone survey found that 34% of Americans had used at least one or more questionable health care treatments in the past year, whereas more than a third of these had seen providers for unconventional therapy.[2] In both the United States and Canada, quackery has become a multibillion-dollar industry. As a result, an army of multilevel marketing entrepreneurs, health food store operators, and nonscientific health care providers are available to mobilize whenever attempts are made to regulate the use of vitamins, herbs, dietary supplements, or other unproven products.[9]

Although conventional health care seeks to explain illness on the basis of a biomedical model, much nonscientific cancer therapy has its origins in "vitalism," or a common-sense model of disease that the general public finds appealing (Table 1).[11,12] Vitalism is the belief that various "life forces" are the ultimate determinants of health or disease. Patients with cancer are thus informed that their disease has resulted from a failure to eat and exercise in accordance with nature's laws, but that the body's defenses can be rejuvenated and harmonized by exercise, diet, and stress reduction.[11] A holistic approach that includes meditation or imagery therapy, diet, and exercise is offered as an alternative to what may be perceived as an impersonal and disease-oriented medical system. Many alternative cancer treatments involve the use of specific diets that are said to detoxify or cleanse the body.[13]

Other treatments advocate a comprehensive philosophy or behavior system such as is incorporated in Ayurvedic medicine or traditional Chinese medicine. Patients today are well aware of possible unpleasant side

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effects associated with chemotherapy or radiation treatment. Natural approaches such as herbal therapies or the use of vitamins are touted as side-effect-free methods for strengthening a person's intrinsic defenses by boosting the immune system.[6,7] Such nontoxic-appearing, natural therapies are intuitively satisfying to patients who naively imagine that nature is always kind and gentle. Further empowering the nature of such therapies is that they stress the role of patients as their own therapist and appear to provide patients with a degree of control over their disease processes. Such concepts fit in well with the current general mistrust of authority and institutions and the prevalent "take charge, do it yourself" attitude.[1] The most common reasons cited by individual cancer patients who seek out unproven therapies have been well documented (Table 2).[10]

Studies of the social and demographic background of persons embracing unproven therapies have shown that they tend to be better educated with higher-than-average incomes.[6] As an example, the British royal family has expressed an ongoing interest in alternative medicine. Prince Charles made a special trip to assist at the opening of the Bristol Cancer Health Centre, a facility in the United Kingdom that specializes in unorthodox therapy. The major consumers of vitamins and health food supplements also tend to be financially well-off, educated, middle-class persons.[11]

Possible Toxicity of Unproven Therapy

The range of unorthodox therapies available today is staggering.[8,9,14] These are partially categorized in Table 3. Unfortunately, many of these unproven therapies are not necessarily benign. Laetrile (*l*-mandelonitrile-β-glucuronic acid; amygdalin) contains cyanide that has caused deaths.[15] Intravenous hydrogen peroxide therapy has resulted in severe hemolysis and cardiopulmonary arrest.[16] Vitamins and minerals, which are physiologically active chemicals, are recognized to have toxic effects at high doses, especially in the case of the fat-soluble vitamins A, D, and K.[17] But even the water-soluble vitamins are not without danger when consumed in large doses. The use of vitamin B_1 (thiamine) has been associated with cardiovascular toxicity, including cardiac arrhythmias, edema, and vasodilation.[18] Because the product is available in 100- to 500-mg pills, the consumption of a toxic dose of several grams a day is not difficult. Large doses of vitamin B_6 (pyridoxine) have been associated with peripheral neuropathies.[18] Megadoses of vitamin B_3 (niacin) have liver toxicity and have produced acid peptic disease, myocardial infarct, gouty arthritis, glucose intolerance, hyperkeratosis, and skin rashes.[18] Adverse effects that have rarely been reported with megadoses of vitamin C include hyperoxaluria, nephrolithiasis, and renal sodium loss.[19] It is also important for clinicians to remember that regular vitamin C consumption can interfere with dipstick testing for glycosuria and hematuria and cause false-negative results with the test cards used for detecting occult blood in stool. The consumption of the amino acid tryptophan was recently linked to a newly described, possibly fatal muscular disease, the eosinophilia-myalgia syndrome.[20] Fortunately, the number of cases in Canada was small compared with that in the United States because the sale of amino acid supplements had been banned in Canada.

TABLE 1.—*An Alternative Model of Cancer*

Cancer is a single, simple process that represents symptoms, rather than a disease
Cancer symptoms arise from problems with diet, stress, mental outlook, or the environment
Fitness, nutrition, and mental attitude can fend off cancer; properly motivated cancer patients should be able to mobilize these defenses
Conventional treatments such as irradiation or chemotherapy are toxic and will weaken the body and fail to remedy the underlying disease

TABLE 2.—*Most Common Reasons Given for Using Alternative Therapy*

The appeal of "natural," holistic-appearing remedies as opposed to radiation or surgical therapy or chemotherapy
The possibility of improving quality or quantity of life, especially if told "nothing further can be done"
The need to have a sense of control over life
Possible pressure from family and friends
Mistrust of the conventional medical establishment and authority figures in general

Herbal products available in the form of teas, powders, tablets, and capsules are heavily promoted by pharmacies, supermarkets, and health food stores. Nutritional and body-building magazines also advertise these products. Herbal preparations are typically assumed by the public to be bland because of their natural image. Another myth perpetrated by the promoters of herbal therapy is that organic chemicals produced in nature by the metabolic processes of plants and animals possess an innate superiority over the same products synthesized in chemical laboratories.[21] A second dogma is that whole plants, leaves, or roots have physiologic properties different from the various constituents isolated from the same plant parts.

Herbal preparations may have substantial toxicity. Because they are not regulated by federal or state agencies, usually neither safety nor efficacy have been verified.[22] Given the wide variety of herbal remedies and their inconsistent and multiple ingredients, it may be impossible to identify the toxicity of specific herbal agents. Comfrey tea may cause hepatic veno-occlusive disease, and certain other herbal teas are also rich in hepatotoxic pyrolizidine alkaloids.[23] The spectrum of liver injury associated with the long-term ingestion of hepatotoxic herbal remedies is broad ranging, from mild hepatocyte necrosis to extensive inflammation, cholestasis, veno-occlusive disease, chronic hepatitis, and cirrhosis.[24] It is entirely possible that chaparral or other herbal preparations may be responsible for some cases of cryptogenic

TABLE 3.—*Some of the More Common Questionable Cancer Therapies*

Unproven Therapy	*Major 'Common-Sense' Premise*	*Examples*
Metabolic therapy	Toxins and wastes are cellular poisons, which treatment can detoxify	Laetrile (amygdalin) Iscador or mistletoe Hydrazine sulfate Hydrogen peroxide Dimethyl sulfoxide
Herbal remedies	Herbal preparations have secret, curative properties	Essiac Comfrey Taheebo tea Chaparral tea Pau D'Arco tea Aloe vera Barley green Blue-green algae Beet root juice Hoxsey's Herbal Tonic
Megavitamins	High doses of vitamins can kill cancer cells and rejuvenate tissues	High-dose vitamins C, B, A, D, and E and niacin
Diet therapy	"You are what you eat": a therapeutic diet can balance "out-of-whack" body function	Gerson method Grape diet Macrobiotic diet Coffee enemas Shark cartilage
Electronic devices	Can harmonize the body's "life forces" and cure or prevent cancer	Galvanic therapy Magnetic field therapy Negative ion therapy Color and light therapy
Imagery therapy	Guided mental imagery can destroy cancer cells or arrest cancer growth	Simonton technique
Immune therapy	Cancer thrives due to defective immune mechanisms, which treatments can restore	Autologous and fetal vaccines Burton treatment

chronic hepatitis or cirrhosis.[25] Cases have been reported wherein herbal preparations have been adulterated with other medications such as steroids, phenylbutazone, or warfarin sodium.[26] Whereas limiting the consumption of herbs could be beneficial, this is not likely to occur in the immediate future. Accordingly, practical advice has been developed for those who are determined to use these medications (Table 4).

Diets that have been purported to be curative or beneficial for cancer have been described in a variety of ways, including nutritional, metabolic enzyme, macrobiotic, nontoxic, and oxidative. Coffee and colonic enema therapy has resulted in electrolyte imbalance, bowel necrosis with perforation, toxic colitis, amebiasis, campylobacter sepsis, and dehydration.[27] Bland vegetarian macrobiotic diets may result in hypocalcemia, scurvy, or serious protein fat malnutrition, especially in an already cachectic cancer patient.[13,14] Cases of vitamin B_{12} and iron-deficiency anemias have also been reported as a result of such diets. A macrobiotic program that includes special supplementary tapes, literature, and follow-up can end up costing thousands of dollars. High-fiber macrobiotic diets may be dangerous for patients who have had bowel resections. There is some question that the shorter survival experienced by a cohort of women with breast cancer at the Bristol Cancer Help Centre was in fact related to their macrobiotic diet.[28] Certain cancer vaccines given intravenously as immunoaugmentative therapy have been found to include specimens positive for both the hepatitis B antigen and antibody to the human immunodeficiency virus.[29]

Various electronic devices appear to be making a comeback as bogus cancer treatments. Such therapeutic modalities have included magnetic field therapy, galvanic devices, low-voltage treatment devices, negative ion and ozone generators, and color and light treatments.[30] Electronic devices have a strong appeal to those who adhere to a vitalistic philosophy and who also claim that the well-known patterns found in electrocardiograms or electroencephalograms are expressions of life forces that conventional scientists have failed to fully understand and exploit.

Even mental imagery therapy can occasionally cause problems when used as an adjunct to cancer treatment if patients are left feeling guilty or inadequate when there is progressive tumor growth.[31] Properly used, visualization and imagery techniques should be beneficial because they aid in coping and provide patients a degree of

TABLE 4.—*Practical Advice Regarding Herbal Preparations*

Only buy herbs from reputable stores or dealers
Only buy herbal preparations with the plants listed on the packet
Do not take a large quantity of any one herbal preparation
Do not take any herb on a daily basis
Do not take herbs if pregnant or attempting to become pregnant
Do not take herbs if nursing
Do not give herbs to your children
Do not take anything containing comfrey

control that may decrease feelings of helplessness.[32] Unfortunately, some practitioners of imagery therapy do not blame their therapy when disease progresses, but imply that the users lack discipline or have not followed instructions properly. Personality traits that have been labeled as being responsible for the development and progression of cancer include a limited capacity for trust, a tendency toward self-pity, and the inability to develop long-term relationships.[12] Such blame-the-victim explanations appear to be without scientific merit, as several controlled studies have failed to document the existence of any "cancer-prone personality" or that psychosocial factors in general are correlated with cancer survival.[33,34] Patients with cancer should be made aware that no scientific evidence to date has confirmed that imagery therapy or other alternative treatments have any effect on tumor growth, tumor regression, or overall patient survival.[31,35] Similarly, patients with cancer should not be led to think that their cancer is a punishment for wrong thinking, a weak will to live, or a loser mentality.

Finally, besides the direct physical harm caused by some unproven treatments, as previously discussed, these therapies in some cases may also result in a delay in proper diagnosis, a fatal abandonment of possibly curative treatment, unjustifiable financial or emotional hardship, or even simply the wasting of a patient's valuable remaining time.[6,15] In this sense, some alternative treatments are more restrictive than orthodox treatments could ever be and can seriously interfere with family relationships. It is not surprising that studies comparing orthodox with alternative treatments have shown that the quality of life for those using alternatives may be considerably worse.

Investigators compared the length of survival and quality of life of patients who received unorthodox treatment at the Livingston-Wheeler Medical Clinic, San Diego, California, with those of control patients who received only conventional therapy at the University of Pennsylvania Cancer Center, Philadelphia.[35] Patients at the Livingston-Wheeler clinic were treated with an autologous bacilli Calmette-Guérin vaccine, vegetarian diets, and coffee enemas. In this study, patients were matched according to sex, race, age, diagnosis, and time from diagnosis of metastatic or recurrent disease. The length of survival did not differ between the two groups, but the quality of life was substantially better in the patients receiving conventional care.

Fraudulent Methods of Cancer Diagnosis or Investigation

Bogus and unscientific laboratory investigations constitute an area that has been growing increasingly lucrative in the alternative therapy field.[8,9,30] Their proponents are often slick promoters who use plausible scientific jargon, operate high-tech modern facilities, and boast walls of diplomas.[10] Computerized health questionnaires are widely available that claim to diagnose various nutritional deficiencies, metabolic problems, or the presence of precancerous states based on patient response.[9] Typical questions include "Do you feel chronically tired, crave sugar, or suffer mood swings?" or "Are you subject to frequent viral illnesses?" If a certain number of affirmative replies are generated, the computer program then diagnoses a high probability of yeast infection, hypoglycemia, or premalignancy. This is often followed by a solicitation to purchase various vitamin and dietary aids from the therapist to remedy the situation.

Although hair testing has for years constituted a scientifically valid method for assessing certain heavy metal toxicities, unscrupulous nutritionists claim to be able to use hair analysis results to prescribe replacement dietary supplements that may help to ward off cancer. Cytotoxic testing involves the mixing of food extracts with individual blood specimens, with any changes in agglutination purportedly predictive of food sensitivities or toxicity, allergies, immune deficiency, or a precancerous state. Live blood cell analysis consists of a detailed analysis of an unfixed blood specimen conducted by a sophisticated videocamera microscope. Patients are encouraged to participate in the interpretation with the therapist and also to decide which is the best route to correct any perceived dysfunction of their blood cells and immune system. This analysis is touted as being able to demonstrate the activity or inactivity of the immune system, the presence of live fungi or bacterial forms in the blood, parasites, crystalline structures such as arterial plaque, and other bodily imbalances. Live blood cell analysis costs about $150 for a 45-minute to an hour session and is usually concluded with an invitation to purchase various remedies.

Herbal crystallization analysis involves the drying of a drop of saliva with a drop of reagent on a glass slide. Crystals that form are analyzed for predictive or curative patterns. For instance, the appearance of two parallel lines might be interpreted as representing a blood vessel and the person subsequently advised to take vitamin supplements. With another popular diagnostic system, test tubes containing various extracts and dietary substances in liquid suspension are passed over a cancer patient's sternum. If a tube changes color or appears to be attracted to the sternum, the patient will be diagnosed as allergic to or deficient in the substance in question.[30] Such pseudoscience in the diagnostic field is not limited to patients with cancer. These quasi-diagnostic and other therapeutic methods have been widely used to promote such diagnoses as the chronic yeast syndrome, dental amalgam toxicity, or the total allergy syndrome.[9]

Characteristics of the Promoters of Unproven Therapies

Unlike the proverbial purveyors of snake oil of yesteryear, today's proponents of unproven therapy are well educated and presentable. One study showed that more than 65% of alternative medicine practitioners actually hold an MD or DO degree.[3] In their promotion of unproven therapy, they emphasize testimonials over the results of scientific clinical trials in such a way that the audience hears only of successes.[10] To justify the lack of proper statistical records, the statement is often made that "we are simply too busy treating patients to collect and analyze data." Patients who are repeatedly exposed to testimonial results are usually unaware that the vast majority of those whose condition deteriorated while they were taking the unorthodox therapy in question are no longer available to testify. Scientific follow-up of individual cases involving testimonials has frequently shown that the diagnosis of malignancy was never firmly histologically established or, most commonly, that the person in question also partook of concomitant conventional cancer therapy.[15] At testimonials, however, any successful result is always attributed to the unconventional rather than conventional treatment. Nothing is dearer to the heart of an unorthodox therapist than a Hollywood star or other celebrity with cancer, such as Steve McQueen or Michael Landon. By operating on the principle that any publicity is good publicity, even when the outcome is unfavorable, unorthodox practitioners later claim that the patient in question arrived too late to benefit from their treatments.[7]

In their book *Magic or Medicine?* Buckman and Sabbagh have extensively discussed possible perceived differences between conventional and unorthodox health care practitioners.[36] Table 5 summarizes many of these observations. As Buckman writes,[36(p244)]

> In my medical training, I didn't learn very much about the human qualities that might help me in medical practice. In those days, there was no teaching of "Interpersonal Skills" in the medical school curriculum—and that was a serious omission. I needed to learn more about how to respond to the symptoms of humans at the same time as I treated their diseases. Nowadays, things are changing. Contemporary medical students are taught far more about the human aspects of medicine and about communication and empathic skills than in my day. However, as a group, we conventional doctors have not yet taken this lesson fully on board.

What Conventional Health Care Professionals Can Do

Conventional health care professionals can learn from unorthodox practitioners by embracing those aspects of their treatments that may be beneficial to the therapeutic relationship, such as empathy, continuity of care, and the provision of hope. Health care workers need not specifically share a patient's belief system, but they must understand and respect it for any treatment to be effective. Unconventional practitioners are often seen as positive, empathic, and available, whereas conventional health care professionals may be perceived as neutral, cautious, evasive, or impersonal.[29] Honesty and openness must be used in all discussions with cancer patients. The current lay literature strongly endorses patients' right to the freedom of informed choice. Health care professionals must respect this right with ongoing open and frank discussions.

Initial patient interactions are crucial. Holland and others have recommended that physicians raise the issue of unorthodox treatments routinely with cancer patients at the time of the first visit.[37] This is important because studies have clearly shown that most consumers of unconventional therapy do not mention these treatments to their physicians, suggesting a deficiency in current patient-physician relationships. For instance, one investigation revealed that 75% of 300 informants did not tell their physicians that they were using an alternative therapy.[4] It may well be that this lack of communication derives from physicians' mistaken assumption that most patients do not routinely use unconventional therapies for serious medical problems. In addition, many physicians are reluctant to discuss the use of unconventional therapies because they lack adequate knowledge of these techniques and also think they do not have the time. In either case, such a failure to communicate is not in the best interest of patients.[38] Nurses, social workers, and dieticians may play a key role in this regard, as they are frequently the first to see new cancer patients who may confide to them things they would not tell their physician.

The American Cancer Society is helpful in providing up-to-date information on various alternative therapies. Since 1954, it has maintained a Committee on Questionable (formerly "Unproven") Methods of Cancer Management. Reviews of questionable treatments are published regularly in the American Cancer Society's journal, *CA: A Cancer Journal for Clinicians*.

Rather than being rejected out of hand and thus making a patient feel foolish, unproven therapies should always be discussed objectively. To accomplish this, health care professionals need to be aware of which unproven therapies are in vogue in their particular geographic area. This will necessitate paying attention to news media and having a member of the health care team attend various meetings, symposia, and public lectures. Health care professionals might also consider visiting health food stores to review what products are available. Useful information can be gathered by browsing through the many brochures and leaflets that are for sale or distributed free of charge. Individual patients should be warned that at some point in their illness, they are likely to be approached by well-meaning relatives, friends, or others regarding some type of unproven therapy. At the same time, they should be urged not to turn their back on conventional treatments if they elect to try the unconventional.[10] Because many alternative therapies seem to be lifestyle-oriented, the individual topics of diet, vitamins, and stress reduction should be specifically reviewed early on with each cancer patient.[7] A realistic discussion of foods may prevent patients from sub-

TABLE 5.—*Differences That Patients May Perceive Between Conventional and Unorthodox Therapists**

Perceived Quality	*Conventional Practitioner*	*Unorthodox Therapist*
Time	May be rushed; average 6-10 min/patient	Unrushed; average 90 min for first consultation, 20 per follow-up
Setting	May be depersonalized and institutionalized	Considerable effort made for patient's comfort and personalization
Continuity	Patient may see different person on follow-up visits	Patient usually sees same person
Symptom handling	Trained to interpret patient's symptoms in light of knowledge of underlying disease; may "disbelieve" or contradict patient's perceptions	Accepts patient's symptoms at face value
Emotional handling	Empathic abilities may be lacking	Empathic abilities central to therapist's skill
Dealing with patient's uniqueness	May try to compensate for or minimize personal idiosyncrasies of patient	Therapist regards patient's personal features as central to the illness and its treatment
Dealing with social context	Variable; importance of social context may be ignored or underestimated	Social context regarded as central to understanding of illness
Appearance of certainty	May appear uncertain; obliged to express both sides of any controversy regarding therapy	Absolutely certain and confident; testimonials quoted assure 100% success rate
Ability to give a clear prognosis	Obliged to be statistically accurate; answers may not seem clear or intelligible	Free to deceive—usually provides clear and optimistic prognosis
Ability to provide hope	Variable; may not be a major component of the therapeutic relationship	Usually a major part of the therapeutic relationship

*Modified with permission from Buckman and Sabbagh.[36]

sequently embracing a bizarre diet as well as provide an awareness of a holistic concern for health. A practical approach to vitamin therapy is to point out that whereas the North American diet is usually adequate, moderate extra doses of the water-soluble vitamins such as B and C do not ordinarily constitute a health hazard. The possible dangers of the excessive consumption of vitamins such as A, D, and K should be mentioned, however. Because many patients wonder if a stressful lifestyle was responsible for their tumor, they should be reassured that to the best of our current knowledge, cancer is not related to thoughts, feelings, personality characteristics, or any mental or emotional state.[12,33] At the same time, the benefits of support groups or other patient counseling services should be stressed. Providing advice on relaxation therapy and mental imagery techniques may also enhance a sense of control and emotional well-being.[32]

Finally, patients with cancer should always be left with hope. New patients can be reminded that research is continually providing different therapeutic agents and methods of treatment. Terminally ill patients especially should not be left with a feeling of being hopelessly abandoned, as this may put them at high risk for embracing unorthodox treatments.[39] Appropriate pain and palliative care management, coupled with an empathic approach, may help to facilitate a sense of control and negate possible feelings of rejection.

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Epitomes

Important Advances in Clinical Medicine

Neurology

David P. Richman, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Neurology of the California Medical Association, and the summaries were prepared under the direction of David P. Richman, MD, and the panel.

Neurology of Human Immunodeficiency Virus Infection—Past, Present, and Future

TWO YEARS AFTER THE acquired immunodeficiency syndrome (AIDS) was described, investigators published the first case series reporting its neurologic complications. Cerebral toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary central nervous system (CNS) lymphoma emerged as major cerebral manifestations, suggesting the brain was not spared from the atypical infections and rare tumors that characterized systemic AIDS. New neurologic syndromes were recognized, such as subacute encephalitis and vacuolar myelopathy; AIDS was added to the differential diagnosis in patients with aseptic meningitis and painful neuropathy. Then, as now, in nearly half of patients infected with the human immunodeficiency virus (HIV), clinically apparent neurologic illness developed.

Identification of the pathogen, now known as HIV, and the development of serologic testing in the mid-1980s expanded the spectrum of associated neurologic disorders and provided new clues regarding pathogenesis. Evidence of viral antigens and nucleic acids in the brain supported the notion that subacute encephalitis, clinically manifest in mid- to late-stage HIV infection as dementia, might be caused by HIV. Cerebrospinal fluid pleocytosis in patients with early HIV infection, whether asymptomatic or clinically evident as aseptic meningitis, suggested a possible mechanism for the virus to gain access to the brain. The association of acute and chronic inflammatory demyelinating polyneuropathies with early HIV infection argued that a dysimmune state might precede the overt immunosuppression of AIDS. Other neuromuscular complications were recognized, some infectious (cytomegaloviral [CMV] polyradiculitis and mononeuritis multiplex), some possibly immune-mediated (vasculitic mononeuritis multiplex and inflammatory myopathy), and some idiopathic (nemaline rod-body myopathy). In children with AIDS, encephalopathy, either static or progressive, emerged as the most prominent neurologic manifestation, with opportunistic infections and tumors infrequent, myelopathy rare, and neuromuscular disorders either uncommon or unrecognized.

As nucleoside antiretroviral agents came into use in the late 1980s, attention turned to whether these agents would lessen neurologic disease, particularly diseases thought primarily due to HIV. High-dose zidovudine is effective for HIV-associated dementia in adults and for encephalopathy in children, although it remains uncertain whether didanosine, zalcitabine, or stavudine therapy provide similar benefit. In contrast, myelopathy and painful neuropathy do not respond to standard antiretroviral therapy, and in fact, painful neuropathy is a dose-limiting side effect of the use of didanosine, zalcitabine, and stavudine. Myopathy complicates zidovudine therapy in as many as 30% of patients taking the drug long term. Histologic features suggest mitochondrial dysfunction, and patients often improve after the drug is withdrawn. Ultrastructural changes in mitochondria, along with in vitro studies and studies of animals, further support the concept of zidovudine as a mitochondrial toxin.

The management of neurologic opportunistic infections has been more successful. Sulfadiazine and pyrimethamine for cerebral toxoplasmosis, amphotericin B and fluconazole for cryptococcal meningitis, and ganciclovir and foscarnet for CMV polyradiculitis have made these diagnoses compatible with long-term survival in patients able to tolerate the maintenance therapy these infections require. For patients with progressive multifocal leukoencephalopathy, the prognosis is in months, which is worrisome because this late-stage reactivation of cerebral JC viral infection might be anticipated to become more common as antiretroviral therapy and improved treatment of infectious complications extends the survival of patients with AIDS. Despite advances in treating primary CNS lymphoma in patients who do not have AIDS, the prognosis remains grim in patients with AIDS, in whom aggressive chemotherapy poses high risks.

The disabling, if not fatal, nature of neurologic disease requires continuing efforts to understand how HIV infection and its treatment affects the nervous system, particularly as HIV infection begins to evolve from an imminently life-threatening illness to a chronic condition. Dramatic changes in health care delivery strain practitioners caring for HIV-infected patients, and tight research funding and unprecedented patient activism put pressure on clinical and basic science HIV investigators. Antiretroviral clinical trials should include the monitoring of neurologic status, both to assess whether new therapies are effective against primarily HIV-related conditions such as dementia and to characterize neurotoxic side effects. When rapid changes in AIDS treatment preclude separate follow-up studies to address efficacy and side effects of neurologic importance, neuroepidemiologic surveillance can confirm clinical trial observations. They can also identify risk factors and trends in neurologic disease, which define research and patient care priorities. Basic HIV research has described the neuropathologic substrate for dementia and suggested that the viral-encoded protein gp120 may be neurotoxic, providing intriguing clues about the neuropathogenesis of dementia and neuropathy. Continued advances in HIV molecular and cell biologic processes and increased understanding of viruses and immune responses have the best promise for developing effective treatment of the virus's protean neurologic manifestations. Finally, it is worth recalling that both AIDS and its neurologic sequelae were recognized by clinicians who recorded their observations and appreciated their importance. For the foreseeable future, clinicians will have a place beside the clinical trialists, epidemiologists, and basic scientists in the battle against HIV.

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Emerging Therapies for Acute Stroke

IN THE PAST TWO DECADES, major advances have occurred in stroke prevention, including risk factor intervention, antithrombotic prophylaxis in atrial fibrillation, antiplatelet therapy, and carotid endarterectomy. Nonetheless, with the aging of the United States population, ischemic stroke is an increasingly common, devastating disorder. Fortunately, we are entering a new era of effective interventions for acute stroke that reflects a remarkable confluence of advances in three areas: the pharmacology of hypoxic neuronal injury and of thrombolysis, the diagnostic neuroimaging of patients with early ischemia, and the clinical pathophysiology of the first few hours of stroke in humans.

Two strategies dominate current pharmacologic investigations in acute stroke treatment: cytoprotection and arterial recanalization. Cytoprotective therapies are the product of fundamental neuroscientific advances in identifying at a manipulable, molecular level mechanisms of neuronal injury in hypoxic environments. When focal occlusions disrupt blood flow to the brain, a cascade of molecular events leading to cell injury follows. The release of excitatory amino acid neurotransmitters, the accumulation of intracellular calcium, the generation of oxygen-free radicals, nitric oxide formation, and the release of cytokines by infiltrating polymorphonuclear leukocytes all mediate cellular injury and afford numerous targets for pharmacologic blockade. The *N*-methyl-D-aspartate excitatory amino acid channel alone possesses at least six sites at which competitive inhibition confers neuroprotection in animal stroke models. A multitude of phase II and phase III clinical trials of excitatory amino acid neurotransmitter antagonists, novel opiate antagonists, voltage-gated calcium channel antagonists, and antileukocyte-adhesion monoclonal antibodies are now under way in this country. These studies will ideally yield a combination of complementary neuroprotective agents that may be applied shortly after the onset of a stroke, in the field or on arrival in emergency departments, to preserve cell integrity until measures restoring blood flow can be implemented.

Chief among the concerns hampering the development of arterial recanalization of the cerebral circulation through thrombolysis and angioplasty has been that, unlike the heart, the brain bleeds. Will symptomatic hemorrhages into an infarct bed outnumber the rewarding cases of swift and dramatic neurologic recovery that all centers employing thrombolysis have observed when therapy is initiated within hours after the onset of stroke? Increasing worldwide experience with thrombolytic agents suggests that thrombolysis has the potential to be a double-edged sword, but with net benefits. A just-completed large European trial using tissue plasminogen activator administered intravenously within six hours of an ischemic stroke found a statistically significant benefit of therapy on functional outcome in target patients, with a lesser, countervailing trend of an increased incidence of hemorrhage among patients with subtle computed tomographic (CT) abnormalities not recognized by enrolling centers. The emerging clinical literature suggests that intracranial thrombolysis can reduce infarct size and can enhance neurologic outcome if it is carefully and rapidly delivered. Intra-arterial therapy administered by superselective catheterization of the occluded intracranial artery may allow higher recanalization rates and decreased bleeding complications than intravenous therapy and is the subject of a new multicenter trial with several participating western centers.

Patient selection for neuroprotective and thrombolytic therapies has been limited by the inability of standard CT or magnetic resonance (MR) studies to visualize ischemic changes in the first four hours after onset. Clinical localization, imperfect and highly dependent on experience, currently guides initial therapeutic decisions. Several new

MR techniques, however, promise to increase the capacity to define early changes. Diffusion-weighted imaging measuring translational movements of water detects and localizes ischemic fields within 30 minutes of onset. Perfusion imaging with ultrafast tracking of the passage of a bolus of contrast provides an immediate quantitative assessment of cerebral tissue blood flow and volume. Magnetic resonance spectroscopy allows the tracking of metabolites within neurons that distinguishes normal cells, infarcted cells, and ailing but still viable penumbral cells. At selected centers developing new echo planar hardware, concurrent standard MR imaging, MR angiography, diffusion MR, and perfusion MR imaging can be done in patients with acute stroke in only 12 minutes. The result is a comprehensive pathophysiologic picture of brain anatomy, vessel stenoses, tissue ischemia, and tissue perfusion available in the acute stage to guide therapeutic decision making.

Mobilization of the clinical care system for patients with acute stroke is necessary for emerging therapies to be applied. The few studies in animals and humans that have examined the duration of focal ischemia required to produce irreversible neuronal damage suggest that the therapeutic window for brain resuscitation is brief, between one and six hours after onset. In the past, however, the identification, triage, and treatment of patients with ischemic stroke have rarely been rapid, and most patients had therapy initiated after this window had closed. Clinical centers participating in trials of cytoprotective and thrombolytic therapies have shown that intensive education of the public and referring physicians, the development of dedicated stroke teams and units, and the institution of code stroke protocols may dramatically reduce delays to patient presentation, emergency evaluation, and the initiation of treatment. The optimal delivery of current therapies and continued progress in developing promising new therapies depend on galvanizing the medical system to approach stroke like trauma, as a treatable, rapidly evolving neuroemergency.

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Development of Botulinum Toxin Therapy

OVER THE PAST TEN YEARS, the use of botulinum toxin has become well established as safe and effective for the treatment of the involuntary muscle contractions of dystonia and also for the disorder known as hemifacial spasm. Indeed, botulinum toxin injections have become regarded by many practitioners as first-line therapy for hemifacial spasm and focal dystonias such as involuntary, forceful eye closure (blepharospasm); spasms of the vocal cords (spasmodic dysphonia); and involuntary turning or posturing of the head and neck (torticollis). The toxin is also used routinely for focal action dystonia such as writer's cramp and oromandibular dystonia such as involuntary jaw closure. There is also continued use of botulinum toxin in its first clinical application, the nonsurgical treatment of strabismus.

Botulinum toxin works its clinical effect after intramuscular or subcutaneous administration by binding to the nerve endings within muscle tissue and ceasing the nerve's release of acetylcholine to the muscle receptors, resulting in reduced muscle contractions. This effect gradually wears off after a period of typically three to five months as the nerve ending sprouts new connections to reinnervate the muscle. Eventually the nerve-to-muscle connections are sufficiently reestablished to again produce unwanted muscle contractions, and readministration of the toxin is necessary.

Botulinum toxin can be identified by serologic assay as to various subtypes A through G. Type A is the toxin currently available for clinical use. The production of antibodies directed against botulinum type A has been identified in a small percentage of patients receiving the agent and may be related to dosage and the frequency of administration. This antibody production is suspected to be a reason that some patients who initially show improvement with the toxin have a lesser or absent benefit with later administrations. Alternative botulinum serotypes, specifically types B and F, have been examined for use in patients who have had an initial poor response. Reports on the use of type F toxin to treat torticollis indicate that, although of benefit, it has a much shorter clinical duration of about a month.

Side effects of the drug, if they occur, usually are attributable to excessive weakening of the muscle in which the drug is administered, and this is transient as the effects of the toxin wear off. The toxin does appear to have some hematogenous spread. Sensitive measurements of the neuromuscular junction in muscles distant from the administration site have shown that there is a remote although subclinical effect of the toxin. There have been no reports of clinical botulism occurring after the intentional administration of the toxin.

Botulinum toxin has provided a means to treat numerous conditions that have been poorly responsive to medical therapy, or an adequate response often meant the patient had to endure unpleasant side effects of the medicines or surgical treatment. The use of the toxin requires knowledge of its pharmacology and clinical expertise in the movement disorder and muscle anatomy and other conditions for which the toxin has been shown to be beneficial.

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Multiple Sclerosis

MULTIPLE SCLEROSIS is an inflammatory disease of the central nervous system (CNS) of unknown cause. It is a cause of substantial morbidity, affecting about 250,000 young adults in the United States. Epidemiologic studies strongly suggest that the disease is related to an environmental agent, possibly viral, in persons who have a genetic susceptibility due to their major histocompatibility (MHC) molecules. It has been suggested that the putative agent's ability to trigger an autoimmune response in this context is related to acquisition of the agent at a later age in areas that carry a high incidence. The disease is characterized by recurrent episodes of perivenular inflammatory lesions affecting predominantly white matter and resulting in demyelination. The episodes of demyelination are often, though not necessarily, associated with clinical exacerbations of disease.

The natural course of the disease is unpredictable in individual patients, and relapses are often followed by partial or complete clinical remission, resulting in a relapsing-remitting pattern. With recurrent episodes, however, neurologic dysfunction may become irreversible and even progressive. This form of the disease is characterized by a growing number of demyelinating lesions, known collectively as the burden of disease, an increased likelihood of spinal cord involvement, and pathologically with oligodendroglial cell and neuronal cell loss, associated with a lack of remyelination and gliosis.

Until recently, no form of therapy in multiple sclerosis was known to affect the natural history of the disease. Three advances have led to new, promising opportunities for intervention. First, the abnormalities in the immune system, both systemically and in the CNS in patients with multiple sclerosis and parallel abnormalities in experimental animal models have been identified, and they show an overactivity of a subset of $CD4^+$ T-helper cells known as Th1 cells. These activated T cells, present systemically in patients with multiple sclerosis, secrete interferon gamma (IFN-γ). Their activation is dependent on cytokine interleukin (IL)-12 secreted by macrophages and inhibited by cytokines IL-10 and IL-4. Activated T cells pass into the CNS through the blood-brain barrier with apparent ease. Their persistence in the CNS may depend on a subpopulation of these T cells with specificity for CNS antigens, most notably to peptide components of myelin. The pathogenesis of the inflammatory lesions or plaques depends on the activation of macrophages by IFN-γ leading to phagocytosis and the secretion of cytokines, most notably tumor necrosis factor α, that are toxic to myelin. The administration of IFN-γ and increased secretion of endogenous IFN-γ, such as by intercurrent infections, result in exacerbations of the disorder.

A second important advance, brain magnetic resonance (MR) imaging, has proved to be a sensitive detector of demyelinating lesions, and moreover, the concomitant administration of gadolinium allows the detection of the breakdown of the blood-brain barrier as a consequence of active perivenular inflammation. This imaging has substantially influenced the diagnosis of the disease. Equally important, it allows disease activity to be followed in an individual patient.

A third important advance has been the establishment of the double-blinded, placebo-controlled, multicentered clinical drug study as the standard to test efficacies of new medications. This approach has proved important in multiple sclerosis, where the natural history of the disease is variable. The application of these three sets of advances has led to the testing of interferon beta (IFN-β) in patients with relapsing-remitting disease and to the identification of a substantial reduction in the relapse rate and new demyelinating lesions on MR. The mechanism of action of IFN-β appears likely to be related to its in vitro effect in blocking the stimulation of MHC molecules by IFN-γ. Interferon beta has proved fairly safe. The continued occurrence of inflammatory lesions, however, seems to be the basis of a continued progression of disease, albeit at an apparently lower rate.

Other immunosuppressive and immunomodulating agents presently under study may provide synergistic effects by interacting with different facets of Th1 and macrophage activation and function. The effective management of patients with multiple sclerosis is consequently likely to involve the use of combinations of drugs that are able to convey efficacy and relative specificity.

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Dementia—An Update

THE PUBLIC HEALTH IMPORTANCE OF Alzheimer's disease has led to an intensive effort to understand its causes and pathophysiology that is now beginning to yield important results. Most autopsy series of dementia show that Alzheimer's disease is by far the most common cause of dementia in adults, and most older adults who have a slowly progressive decline in cognition that progresses to an overt dementia usually suffer from Alzheimer's disease. Thus, the efforts aimed at improving our understanding of the clinicopathologic correlations, genetics, diagnosis, and treatment of this disease have profound consequences for patient care.

Although there is some controversy about how to diagnose Alzheimer's disease during life, clinicopathologic series generally indicate a substantial validity of the clinical diagnosis, usually between 85% and 100% in

centers using research criteria for diagnosis. The accuracy of the diagnosis of other common causes of dementia, notably dementia due to multiple cerebral infarctions (multi-infarct dementia or ischemic vascular dementia) has generally been considerably lower. The lack of clear criteria for the clinical diagnosis of vascular causes of dementia is likely one reason for this problem, and this has recently been addressed with the proposal of several still-unvalidated schemes for diagnosing and classifying this disorder. Another area of possible importance is the recognition of the overlap, both clinically and pathologically, between Alzheimer's and Parkinson's disease. Many demented patients are found at autopsy to display Lewy bodies in the substantia nigra and cerebral cortex. Often these findings are seen in conjunction with neuritic plaques and neurofibrillary tangles sufficient to diagnose Alzheimer's disease as well. These cases may be called Lewy body dementia, the Lewy body variant of Alzheimer's, or Parkinson's disease with Alzheimer's disease, depending on many factors. These include the clinical presentation, relative degree and location of Alzheimer's and parkinsonian pathologic processes, and the specific neuropathology laboratory involved. Although there is currently no consensus about the terminology and relevance of these findings, there is general agreement that these cases are commonly seen and probably underdiagnosed.

Another important area of research has been the genetics of Alzheimer's disease. It has long been known that in patients with the Down syndrome living to the third decade, the neuropathology of Alzheimer's develops. This information has focused considerable attention on chromosome 21 as a possible etiologic factor. Chromosome 21 has also been known to contain the gene for the amyloid precursor protein (*APP*), the larger protein that is processed to yield β-amyloid, the key constituent of the neuritic plaque. In 1991 an autosomal dominant form of early-onset Alzheimer's disease was linked to mutations in this *APP* gene on chromosome 21, for the first time providing definitive evidence of a genetic cause of Alzheimer's disease, although families with this form of the disease account for a small proportion of all cases of Alzheimer's. Another group of families with early-onset autosomal dominant Alzheimer's disease has been genetically linked by mapping studies to chromosome 14. The identity of this gene has recently also been determined, offering the promise of defining the mechanism of this type of Alzheimer's. Finally, a third Alzheimer's gene has been suspected to reside on chromosome 19, based on population studies in cases of older-onset disease. It now appears that the gene involved is the gene for apolipoprotein E (*APOE*), a protein known for many years to be involved in cholesterol transport. Of the three isoforms, 2, 3, and 4, the last allele, ε4, is associated with an increased risk of Alzheimer's disease. This genetic marker, however, is more properly considered a risk factor for Alzheimer's than a causal gene because in many persons homozygous or heterozygous for the ε4 allele, Alzheimer's disease does not develop.

This genetic information has a number of important consequences for our understanding of Alzheimer's disease. First, it is apparent that the disease is genetically heterogeneous. There are likely to be other genetic causes still undetected, and many cases may not be genetically determined at all. Second, although the appearance of genetic markers offers new possibilities for diagnosis, this use of genetics has considerable problems. Because of the heterogeneous nature of Alzheimer's, the absence of a single genetic marker in a patient cannot be taken as strong evidence against the disease, and the use of *APOE* gene testing as a diagnostic tool is unsatisfactory because it is not invariably associated with the disease. Most important, genetic testing for an incurable disease late in life is of questionable utility. At this point, genetic information is much more important in identifying the cause and mechanisms of sporadic Alzheimer's disease. For this reason, the gene products determined by the Alzheimer's-associated genes are being intensively investigated with respect to their roles in the formation of the amyloid plaque and neurofibrillary tangles characteristic of this disease.

The treatment of Alzheimer's disease has now progressed to the point where specific pharmacotherapy is available. Tacrine, a cholinesterase inhibitor, has been approved for the treatment of Alzheimer's as a result of several placebo-controlled studies. This drug treatment is based on the well-established finding of severe neurodegeneration in the basal forebrain cholinergic system of patients with Alzheimer's disease, with a corresponding diminution of brain acetylcholine. Although the drug provides symptomatic improvement in some patients, enthusiasm for its use has been tempered by the frequent appearance of liver function abnormalities—requiring regular monitoring of serum aminotransferase levels—four-times-a-day dosage, and the transient nature of improvement. Nevertheless, patients able to tolerate the drug at high doses have shown substantial, albeit transient, improvement in cognitive tests. The scientific advances in understanding the pathophysiology of Alzheimer's disease should eventually permit the development of drugs that directly target the relevant pathologic processes in this disease and halt or prevent the development of symptoms.

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Headache

RECENTLY THERE HAS BEEN A notable resurgence in research activity to clarify the fundamental mechanisms of migraine headache. Most of these studies have dealt with the role of serotonin (5-hydroxytryptamine [5-HT])

receptors. Several subgroups of the receptor sites have been identified. The 5-HT1D and 5-HT1B receptors appear to be the most important sites in the pathogenesis of migraine. Another study measuring cerebral blood flow using positron emission tomographic scanning has revealed a progressive reduction in the blood flow originating from the occipital region and spreading anteriorly during the headache, which resembles Leão's spreading depression. These two observations challenge the time-honored concept of the vascular theory of migraine; at the same time, investigators have also demonstrated that antimigraine drugs that act at serotonin-receptor sites also prevent the neurogenic inflammation of blood vessels mediated by substance P-containing nerve fibers in the trigeminal vascular system.

The recent introduction of sumatriptan succinate represents the most important advance in the treatment of migraine headache in several decades. This drug was designed specifically to be active at serotonin-receptor sites and acts as a selective agonist at 5-HT1D receptors, causing vasoconstriction of cephalic vessels. The drug also acts at the presynaptic 5-HT1-like receptors of the sensory nerve endings to block "neurogenic inflammation." This observation has led to a reevaluation of the other commonly used drugs like ergotamine tartrate and dihydroergotamine mesylate. These drugs have now been shown to be active at the same receptor sites.

Sumatriptan is effective in controlling an acute migraine headache—and cluster headache, even though it has not been approved by the Food and Drug Administration for this indication—in more than 75% of patients. The response is so specific that some headache specialists think that the diagnosis should be reevaluated if the drug is not effective. A definite advantage over the conventional medications is that it is effective at any stage of the headache, but there is a high recurrence rate (almost 40%), probably related to the short half-life. Most patients experience cephalic symptoms of burning and tingling, and at least a third of patients complain of tightness of the throat. This last symptom is thought to be caused by spasm of the pharyngeal and esophageal muscles. These effects are short-lived. Uncontrolled hypertension, coronary artery disease, and basilar and hemiplegic migraine are contraindications for the use of this drug. A few deaths have been reported. These were from cardiac causes and mostly were in patients in whom the underlying cardiac disorders were unrecognized.

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New Antiepileptic Medications

SINCE AUGUST 1993, three new antiepileptic medications have become available: felbamate, gabapentin, and lamotrigine. Together they represent a new generation of medications, characterized by less neurotoxicity and poorly understood mechanisms of action compared with older antiepileptic drugs. Although their indications are similar, their unique pharmacokinetic and toxicity profiles are likely to dictate preferences.

Gabapentin is indicated for the adjunctive treatment of partial seizures with or without secondary generalization. Pharmacologically, it embodies many properties of an ideal anticonvulsant. It is not bound to protein, not metabolized, is without drug-drug interactions, and has a high therapeutic index. For these reasons, gabapentin is ideal for use in elders and in polytherapy. Three-times-per-day dosing is necessary, however, because of a half-life of five to seven hours. Somnolence, dizziness, and ataxia are common side effects, but gabapentin can be rapidly titrated with good tolerance. Postmarketing clinical experience suggests that the maximum recommended dosage of 1,800 mg per day may be subtherapeutic and that dosages upwards of 3,600 mg per day to 4,800 mg per day may result in better seizure control.

Lamotrigine has been approved by the Food and Drug Administration for the adjunctive treatment of partial seizures in patients aged 16 years and older. Experience from its extensive use in Europe suggests, however, that it may have a broad spectrum of antiepileptic activity, similar to valproic acid, in the treatment of generalized seizure disorders and the Lennox-Gastaut syndrome. Lamotrigine can be involved in drug-drug interactions because of its hepatic metabolism. Enzyme-inducing antiepileptic medications, such as phenytoin, carbamazepine, and barbiturates, will halve its natural half-life of 25 hours, and valproic acid will almost triple it. Because of the nausea associated with higher doses, twice-a-day dosing is recommended. Its side effects include diplopia, drowsiness, and ataxia. Rash, rarely leading to the Stevens-Johnson syndrome, is a possible risk but may be minimized by avoiding the concomitant use of valproic acid and "starting low and going slow" in escalating the dose.

Felbamate is indicated for use as monotherapy or adjunctive therapy in patients with partial seizures with or without secondary generalization and as adjunctive therapy in patients with the Lennox-Gastaut syndrome. Its use has been complicated by drug-drug interactions and idiosyncratic reactions, namely aplastic anemia and hepatotoxicity, sometimes with fatal consequences. The risk of aplastic anemia, presently estimated at 1 in 3,500, is alarming when compared with the 1 in 40,000 to 1 in 100,000 risk of aplastic anemia associated with the use of chloramphenicol. The manufacturer's recommendations that blood cell counts and liver enzyme levels be measured weekly or biweekly and that consent forms printed on package inserts be signed by patients taking felbamate further restrict its use to patients whose seizures are refractory to other medications. The lesson set forth by felbamate is that any antiepileptic medication has the potential for idiosyncratic reactions.

The role of new antiepileptic medications in the face of more established drugs will surely evolve as more experience is gained in their use. At present, however, they are most likely to be beneficial as adjunctive therapy

for partial seizure disorders and the Lennox-Gastaut syndrome, when indicated.

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ADVISORY PANEL TO THE SECTION ON NEUROLOGY

Alerts, Notices, and Case Reports

Glutaraldehyde Proctitis

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Every hospital should have a plaque in the physicians' and students' entrance: There are some patients whom we cannot help; there are none we cannot harm.
ARTHUR L. BLOOMFIELD, MD[1]

THE USE OF flexible sigmoidoscopy has been recommended for screening patients aged 50 and older for colorectal adenomas and cancer.[2] The technique of this examination can be mastered in 20 to 30 training sessions, and thus it is being increasingly used by primary care physicians.[3] Flexible instruments must be carefully cleaned and disinfected after each procedure.[4] We have recently diagnosed three cases of acute proctitis due to glutaraldehyde, a commonly used disinfectant. Although this is a rare complication of flexible sigmoidoscopy, if unrecognized, diagnostic and therapeutic confusion may result.

Report of Cases

Patient 1

The patient, a 56-year-old woman, came in for sigmoidoscopy as part of a physical examination. She was healthy and had no gastrointestinal complaints. Flexible sigmoidoscopy was done with normal results to 50 cm. Eight hours later, she noted tenesmus and bloody diarrhea. The examination was not repeated. She was started on hydrocortisone enemas (Cortenema) once a day and within three days was asymptomatic. Over the next 12 months, she has remained well.

Patient 2

The patient, a 53-year-old man, had flexible sigmoidoscopy as part of an executive health examination. There was no history of gastrointestinal disease. The results of sigmoidoscopy were normal to 40 cm. The next day, he began having abdominal cramps and bloody diarrhea. He returned to the clinic the following morning or 48 hours after the initial examination. A second sigmoidoscopy revealed erythema, edema, and large ulcers to 12 cm. He was treated with a regimen of oral prednisone and metronidazole (Flagyl). Two days later, the patient was asymptomatic and has remained so over a two-month period.

(Babb RR, Paaso BT: Glutaraldehyde proctitis. West J Med 1995; 163:477-478)

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Patient 3

This 34-year-old woman had colonoscopy done because of a history of ulcerative colitis. She was asymptomatic and took sulfasalazine (Azulfidine). Results of the examination and colon biopsies were normal. Two days later she had abdominal cramps and bloody diarrhea. The sigmoidoscopy was repeated and revealed erythema and multiple ulcers in the distal rectal and lower sigmoid regions. Stool cultures were negative for pathogenic bacteria. A regimen of hydrocortisone enemas (Cortenema) and ciprofloxacin hydrochloride (Cipro) was started. Another sigmoidoscopy four days later showed some healing but a new rectal ulcer. Prednisone and metronidazole were added to her treatment program. Within a week she felt well, and the drugs were stopped. She has been asymptomatic for four months.

Discussion

To prevent infection during endoscopic procedures, guidelines for cleaning and disinfection have been published.[4,5] After its use, the flexible sigmoidoscope should be immediately cleaned with a detergent or cleaning solution and then washed with water. Next, the instrument is immersed in a disinfectant such as glutaraldehyde for a given period of time, then rinsed free of residual germicide, and finally air dried before storage. This entire process can be done by nurses, technicians, or by an automatic washing machine.

In 1986, 13 cases of patients who had proctitis after an initial normal colonoscopic examination were described.[6] The suggested cause was residual cleaning solution in the colonoscope air channel. Two years later, a similar case was reported.[7] In 1992 possible causes of bloody diarrhea in ten patients following normal sigmoidoscopic examinations in an outpatient hospital clinic were investigated.[8] The investigators found that a technician had inadequately cleaned the sigmoidoscopes; they surmised that residual glutaraldehyde in the cleaned instrument had led to acute proctitis. The same authors administered glutaraldehyde to rat colons and noted acute mucosal damage with microscopic inflammation and necrosis. In another report, six patients with acute proctitis after a normal sigmoidoscopic examination were studied.[9] Rectal biopsies showed inflammation, at times accompanied by necrosis and pseudomembranes. Further investigation showed a breakdown in the disinfection cycle of an automatic washing machine and later inadequate air drying of the sigmoidoscopes by the endoscopy staff, so that residual glutaraldehyde remained in the cleaned instrument. More recently, four patients have been described in whom acute proctitis developed after a normal sigmoidoscopic examination.[10] Rectal biopsies demonstrated acute, severe inflammation similar to that seen in acute ischemic injury. Investigation into the cause revealed that cleaning pro-

cedures did not dry the sigmoidoscope channels completely, thus leaving residual glutaraldehyde that was later sprayed onto rectal mucosa. In one patient, the glutaraldehyde was found in the tubing that connected the water bottle to the flexible sigmoidoscope.

Our three patients had the previously described features of glutaraldehyde proctitis. They were asymptomatic before the examination, and the results of the examination were normal. Yet, within hours of the examination, they had acute tenesmus and bloody diarrhea. They were treated with various medications, and all became well within a brief period of time and have remained so. We have since reviewed our cleaning protocol with staff nurses, making certain that the sigmoidoscope channels are flushed free of glutaraldehyde before drying.

Although glutaraldehyde proctitis is rare (we have recognized 3 cases in about 2,400 examinations over the past year), this complication of flexible sigmoidoscopy should be remembered to avoid diagnostic confusion with proctitis due to infection or inflammatory bowel disease. Patients may feel ill, but the prognosis is good, with complete recovery in a few weeks. Various methods of treatment have been used, including oral 5-aminosalicylic acid,[9] antibiotics,[10] steroid enemas,[10] and combinations thereof. It is unclear as to which drug should be recommended, and some patients get well without any specific medication.

Staff members with the responsibility for cleaning instruments should be well trained, disciplined, and thorough.[11] Cleaning and disinfection methods should be reviewed periodically to prevent infection or mucosal damage from disinfectant solutions.

A new type of sigmoidoscope has recently been introduced that avoids cleaning procedures entirely (Vision System, Vision Sciences, Inc, Natick, Massachusetts). A core endoscope is inserted into an Endosheath that contains the usual three channels for biopsy and suction, air, and water. After its use, the Endosheath and its covering are discarded and a new sheath installed for the next patient. The cost-effectiveness and role of this new system are currently unclear.

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Adult Obstructive Sleep Apnea With Secondary Enuresis

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SLEEP APNEA represents a group of sleep-associated respiratory disorders. Apneas—defined as the cessation of airflow for at least 10 seconds—either central, obstructive, or mixed, may occur hundreds of times a night, resulting in asphyxia and disrupted sleep.[1] Although patients with the obstructive sleep apnea syndrome (OSAS) typically are middle-aged, obese men with a short, stout neck, a small posterior oropharynx, a history of snoring, and daytime somnolence, this condition may also be seen in children and nonobese adults.

Affected adults characteristically experience an insidious onset of daytime hypersomnolence. As the disorder progresses, they may have deteriorating memory, concentration, and judgment and personality and mood changes.[1] Family members and bed partners are often the first to recognize these changes, and they relate a history of loud snoring and periodic apneas or choking episodes.[2]

The mortality rate of untreated OSAS has been correlated with apneic events and may be as high as 37%.[3] Untreated OSAS may lead to motor vehicle accidents, polycythemia, systemic hypertension, left ventricular dysfunction, myocardial infarction, cardiac arrhythmias, pulmonary hypertension, cor pulmonale, cerebrovascular accidents, and sudden death.[2,4] Various less commonly appreciated symptoms have been reported, including night sweats, nocturia, nocturnal gastroesophageal reflux, decreased libido, impotence, morning headache, anoxic seizures, and hearing impairment.[4-7] We present a case of obstructive sleep apnea in a patient who presented with the unusual manifestation of secondary enuresis.

Report of a Case

The patient, a previously healthy 26-year-old man, was seen for a general physical examination. A review of systems revealed an 18-kg (40-lb) weight gain over the preceding four to six months. In addition, the patient reported three episodes of enuresis occurring over the previous

(Brown MA, Jacobs MB, Pelayo R: Adult obstructive sleep apnea with secondary enuresis. West J Med 1995; 163:478-480)

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
OSAS = obstructive sleep apnea syndrome

month. He snored intermittently in his late teens, but the snoring had become louder over the past two to three years. Associated symptoms included bruxism, restless sleep, and daytime sleepiness. There was no history of tobacco, alcohol, or other drug use, cold intolerance, polyuria, polydipsia, dysuria, or depression. His family history was notable for two cousins who suffered strokes in their 30s.

On examination the patient weighed 106 kg (234 lb) and measured 168.5 cm (5 ft 6 in); blood pressure was 150/90 mm of mercury, and pulse rate was 82 beats per minute. The patient was alert and attentive. He had retroposition of the mandible and a narrow upper airway with enlarged tonsils, an elongated uvula, and redundant soft tissue of the oropharynx. His hard palate was elevated and narrow. The neck was thick and short. The neurologic and urologic examinations revealed no abnormalities. Laboratory studies elicited normal values for thyroid-stimulating hormone, free thyroxine, serum creatinine, electrolytes, blood glucose, and urinalysis. Over the next three months, he progressed to where he was having almost nightly enuresis.

Because of a suspicion of obstructive sleep apnea, a referral was made to the Stanford University Sleep Disorders Clinic. On nocturnal polysomnography, the patient was observed to have hypopneas and apneas with subsequent oxygen desaturation to 46% and a maximal esophageal pressure recording of −140 cm of water (normal, 10 cm of water). The patient had an average of 48.1 apneas per hour and a respiratory disturbance index of 75.1. Continuous positive airway pressure (CPAP) was titrated to 13 cm of water, with improvement in the patient's sleep. At a five-month follow-up, the patient reported improved daytime alertness and complete resolution of the enuresis.

Discussion

Obstructive sleep apnea is a major health problem in the United States, affecting at least 4% of middle-aged men and 2% of women aged 30 to 60 years.[1] Every primary care provider can expect to see patients with this condition. Patients are often overweight but can also be normal or underweight, particularly younger patients. Apneic episodes are characteristically much worse during rapid-eye-movement sleep because of the associated atonia of accessory respiratory muscles during this part of the sleep cycle. Risk factors for the disorder include a family history, craniofacial anomalies, obesity, and advancing age.[2,6]

In children, secondary enuresis is a common, well-recognized presenting symptom of obstructive sleep apnea and improves with CPAP therapy or adenotonsillectomy.[8] In adults, however, secondary enuresis due to obstructive sleep apnea is both less common and less well recognized. This symptom in adults was not described in several recent reviews,[1-3,9] but has been mentioned in others.[4,5] Secondary nocturnal enuresis in adults with normal urologic evaluations has been noted in patients with obstructive sleep apnea since at least 1976[10]; yet, it is not well recognized by primary care providers. The differential diagnosis of adult secondary enuresis includes diabetes mellitus, lower urinary tract infection, degenerative neurologic conditions, or psychological factors.[11]

Nocturnal enuresis was noted in 7% of 120 adult patients with OSAS in one series.[5] The mechanism for nocturnal enuresis in this disorder is not clear and may be multifactorial. Patients have been shown to have increased urine production and salt excretion and tend to have more frequent nocturnal micturitions during sleep that normalize after treatment with nasal CPAP.[7] This was related to possible increased atrial natriuretic peptide release or to decreased activity of the renin-angiotensin-aldosterone system.[7] The increased urine production and salt excretion may explain why patients with obstructive sleep apnea also have symptoms of nocturia. Another possible explanation may lie in the hypercatecholamine state of apnea, producing a fight or flight autonomic surge with changes in the autonomic control of vesical muscle. Abnormal sleep, the associated confusion, and the increase in intra-abdominal pressure have also been speculated as causes of enuresis.[5]

The role of increased intra-abdominal pressure in nocturnal enuresis is supported by a case in which the authors measured the cystometric pressure in a middle-aged obese woman with severe obstructive sleep apnea and nocturnal enuresis.[12] Increased pressure waves were associated with the apneic events. A loss of posterior urethrovesical angle and an increase in intra-abdominal pressure caused by respiratory efforts against a closed upper airway were suggested to play an important role in the occurrence of enuresis in that case. The authors found a decreased number of apneic and enuretic episodes along with smaller cystometric pressure waves following weight loss and treatment with imipramine hydrochloride and acetazolamide. The sleep apnea and the enuresis did not completely resolve with the treatment, however, and a trial of CPAP was not reported.[12]

In our patient, the abnormal esophageal pressure was corrected with CPAP, with the enuresis resolving. The increased work of breathing against a narrow airway causes the increase in esophageal and intra-abdominal pressure. The mechanism of nocturnal enuresis in patients with obstructive sleep apnea may be the combination of increased urine production, with increased intra-abdominal pressure and distortion of the urethrovesical angle.[12] Decreasing the upper airway resistance corrects the pathophysiologic factors in nocturnal enuresis with obstructive sleep apnea.

Conclusion

Obstructive sleep apnea is a prevalent and possibly serious problem. There are a host of well-known clinical clues that should alert physicians to this diagnosis.

Secondary enuresis, a distinctly uncommon symptom in adults, should be considered a possible marker for this condition. If obstructive sleep apnea is confirmed, an extensive neurologic or urologic evaluation is probably not necessary.

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Toxic 'Sock' Syndrome
Bezoar Formation and Pancreatitis Associated With Iron Deficiency and Pica

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PICA, OR THE INGESTION OF nonfood items, often occurs in patients with iron deficiency anemia and occasionally causes medical complications. We report a case of pica of an unusual substance, athletic tube socks, in a young woman and the subsequent development of a bezoar, pancreatitis, and pseudocysts.

Report of a Case

The patient, a 22-year-old woman, presented to an emergency department because for three weeks she had had nausea, vomiting, and dull left upper quadrant pain radiating to her back. On the day of admission, the pain had become severe and "cramplike," and she noted blood in her vomitus. The patient said she had never had similar pain, pancreatitis, peptic ulcer disease, hepatitis, cholelithiasis, or abdominal trauma. She took no medications on a regular basis and did not smoke or drink alcohol. She had attended college and worked full-time. Of interest, the patient's boyfriend reported that she gnawed on and swallowed athletic-style tube socks to "relax." The patient considered this "a nervous habit" that began five months previously. She estimated that, at the time of admission, she consumed half a sock per evening. She denied having a history of psychiatric problems or of eating clay or other nonfood items. She also reported that she chewed on and swallowed clothing when she was in her teens.

On examination, she appeared anicteric and in considerable pain. Her abdomen was distended, with epigastric and left upper quadrant guarding and tenderness, but there were no signs of peritoneal inflammation, masses, hepatomegaly, or succussion splashes. The findings of a pelvic examination were notable for heavy menstrual flow. Her affect was appropriate.

Laboratory studies elicited the following results: pancreatic amylase, 3,795 U per liter; normal hepatic aminotransferase levels and bilirubin concentration; a leukocyte count of 11.6×10^9 per liter (11,600 per mm^3); hematocrit, 0.31 (31%); and a mean corpuscular volume of 67 fl (67 μm^3). An abdominal x-ray film showed an apparent large gastric mass.

The patient was admitted with the diagnoses of acute pancreatitis, microcytic anemia, pica, and a gastric mass. Esophagogastroduodenoscopy (EGD) revealed a metallic-colored gastric bezoar that extended into the duodenum and that was deemed too large for removal by EGD. An abdominal computed tomographic (CT) scan established extension into the third portion of the duodenum. An abdominal ultrasonogram showed ascites, an edematous pancreas, normal biliary and pancreatic ducts, and an unremarkable gallbladder. Twelve days into her hospital stay, the patient underwent an upper gastrointestinal series with a small bowel follow-through that revealed a persistent gastric bezoar and a separate cecal mass, interpreted as the displaced duodenal portion of the bezoar. A second EGD revealed only the gastric, but not the duodenal, portion of the bezoar. After receiving cathartics, the patient passed a fibrous mass. A gastrotomy for removal of the retained gastric bezoar was canceled because of the presence of pancreatic pseudocysts demonstrated on abdominal CT scan.

On evaluation for anemia, screening was negative for thalassemia. The serum iron level, transferrin saturation, and ferritin level were markedly diminished, and a zinc:protoporphyrin heme ratio was elevated, consistent with severe iron deficiency anemia. A consulting nutritionist found the patient's diet before admission lacking in iron intake.

A team of consulting psychiatrists found no history of a psychiatric disorder and that the patient had been a well-

(Adler AI, Olscamp A: Toxic 'sock' syndrome—Bezoar formation and pancreatitis associated with iron deficiency and pica. West J Med 1995; 163:480-482)

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
EGD = esophagogastroduodenoscopy

adjusted child and strong student who had developed normally. An interview with the patient's mother confirmed that she chewed on clothing as a teenager. On evaluation she was interactive, appropriate, and with coherent thought processes. The patient noted that she began chewing on socks in response to the stress of moving away from her family. She lacked criteria for mood, thought, or anxiety disorders; instead, the psychiatrists thought that she displayed atypical adjustment and impaired coping with stress as manifested by pica.

A month after discharge, an abdominal CT scan continued to show the gastric bezoar. Five months later following iron treatment, the patient said she did not have pica or any abdominal symptoms. An abdominal x-ray film showed no mass. Her hematocrit had risen to 0.37 with a normal mean corpuscular volume.

Discussion

Pica (from the Latin word for "magpie," a bird known for its indiscriminate appetite) is defined as the ingestion of non-nutritive items for at least a month.[1] The description and definition of pica have not changed since Greek times; in English, pica was first described in 1398 and the term first used in 1563.[2] Among those at risk for pica are children, pregnant women, and persons with iron deficiency.[3] The association between iron deficiency and pica is widely recognized, and they were likely related in this case. Pica, including pagophagia or ice eating, frequently resolves with iron replacement therapy,[4] as it did in this case. In a blind study, six of seven subjects stopped their pagophagia following parenteral iron supplementation, compared with none of the subjects who received placebo.[5] Pica is not thought to be compensatory because items eaten rarely provide the lacking nutritive elements,[2,6] which we presume was the case for the socks consumed by our patient. It has been suggested that the iron deficiency-associated buccal changes of stomatitis and glossitis, which probably result from the high iron turnover of these tissues, may drive pica.[7] Because it occurs in patients who are not iron deficient, its cause appears multifactorial and may include social, psychological, and behavioral factors.[2,8]

In this patient, sock eating led to the complication of a bezoar, or a gastrointestinal concretion. The word derives from the Arabic *bazahr*, the hardened contents of the Syrian goat's stomach.[9] Patients with bezoars may have pain, nausea, vomiting, and early satiety. Although our patient had severe pain, nausea, and vomiting, these are also symptoms of pancreatitis, which she had concurrently. In the past, the mortality of nonoperative cases of bezoars exceeded 50%.[10] Hair and plant material typically make up bezoars, but Styrofoam, wool strands, cotton balls, cardboard, and paper tissue have also been reported.[11-13] The bezoar may have worsened the patient's anemia, possibly from diminished iron absorption due to decreased gastric surface area or from gastritis and ulceration. DeBakey and Ochsner, in their review of 250 cases of bezoar, found a prevalence of gastroduodenal ulceration of 15%.[10] If associated with blood loss, ulceration could exacerbate anemia. Although no evidence of ulceration was seen on EGD, the stomach was not fully viewed due to the bezoar, and the presence of blood in the patient's vomitus on the day of admission makes ulceration a possibility.

Of interest is the apparent relationship of the bezoar to acute pancreatitis. Cases of trichobezoar- and persimmon bezoar-induced pancreatitis have been reported.[14,15] In our patient, possible mechanisms include pancreatic irritation from the gastric mass, pancreatic overstimulation, and ampullary blockage by the duodenal segment of the bezoar.

To simulate bezoar formation from tube socks, we performed an experiment using four types of socks composed of varying combinations of cotton, polyester, polypropylene, nylon, acrylic, and Lycra. We placed shredded socks in churning solutions of hydrochloric acid (pH 1.5 to 2.0) for 48 hours in an attempt to reproduce the gastric environment. Results showed negligible dissolution of any sock type, and the polypropylene-containing style aggregated into a ball. The fabric content of our patient's socks remains unknown.

We have presented an unusual case of pica manifested by sock eating, resulting in a bezoar and pancreatitis. This patient's pica may have resulted from her iron deficiency anemia and from impaired coping with stress. The anemia may have resulted from a combination of menstruation, donations to the local blood bank (two) in the year preceding admission (once when she was told she had "borderline anemia"), the bezoar, and an iron-poor diet. Past blood counts were unavailable, so whether the patient's anemia preceded her pica or if she had anemia as a teenager when she also chewed on clothing is unknown. Clinicians should consider eliciting a history of pica in iron-deficient patients with abdominal symptoms.

Acknowledgment

The following persons helped with this case: George Cox, MD; Richard Willson, MD; and Ed Boyko, MD, MPH.

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* * *

A REMINDER

Now that all tubes are out
and the swelling gone
I often curl my tongue inside my mouth
exploring anesthesia's edge.
While on my cheek
I draw my finger
down
the thin
incision line,
turn under the jaw, then up
to my ear
to trace the ragged patch
where touch was carved away.

The textbooks never got it right.
It's not numb, but stands poised
to overamplify the slightest
caress.
And underneath this, a tugging
reminds me that my nerve
is gone—
the one the surgeon sacrificed
to scrape the cancer cells away.

JAY LIVESON, MD©
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Commentary

My Pets, the Spider and the Cricket

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In his declining years, bemoaning his physical deterioration, Michelangelo wrote a poem that included the lines, "A spider's web is hidden in one ear, and in the other, a cricket sings throughout the night."

In this affliction, he was not alone. In one estimate, 40 million Americans are afflicted with this auditory phenomenon, tinnitus, with a substantial proportion of them suffering serious disability.[1]

Beethoven also experienced a constant buzz in his ears, heralding the onset of his progressive deafness. He decried the inability of all the physicians whom he had visited to relieve him of his symptoms. Instead, he accused them of making him worse.

Tinnitus is a word derived from the Latin *tinnere*, meaning "to ring." The term "ringing" is not adequate to describe the variegated forms of this phenomenon. It may be a whistle, a hiss, a roar, a hum, a buzz, a chirp—or a thousand other sounds that intrude where they do not naturally belong. For those afflicted, it is the end of the luxury of silence. It may also be the premonitory sign of a progressive deafness. Deafness, paradoxically, does not ameliorate the tinnitus. The two remain steady partners in this torturous, often maddening malady.

I date the onset of my tinnitus to periods of intense stress occurring almost ten years ago. Mercifully, at that time, the tinnitus was transitory, lasting several seconds to a minute in either ear and appearing at intermittent, unpredictable intervals. It was only about a year ago that I began to experience a continuous, high-pitched ringing in one ear, resembling a flat note on the E string of a violin. Shortly thereafter, I experienced the same phenomenon in the other ear, then in both, with the intensity being greater in one than in the other at any one time.

The constancy of the tinnitus preoccupied me. As a physician trained to attempt a differential diagnosis of all disorders, I naturally put the worst causes highest on the list. I postulated a tumor of the cerebellopontile angle, an acoustic neuroma, a serious metabolic disorder, cerebrovascular dysfunction, or a dozen other worrisome diagnoses.

The first physician I visited did a superficial ear examination, removed some impacted cerumen, ordered audiometric tests, and ended up reassuring me that my ongoing tinnitus was nothing to worry about. I had been hoping that perhaps the cause might be impacted cerumen, but this was not the case. The audiometric tests showed mild depression of acuity in the high-frequency range. To my dismay, the tinnitus continued unabated, reassurance notwithstanding.

As the tinnitus continued, I noted some lessened acuity in my hearing. I began to lean forward to catch some phrases uttered in a casual conversational tone. In noise-filled rooms, whether restaurants, meeting rooms, or hallways, the ambient noise made it difficult to discern words I should have been able to hear without difficulty. In the evenings I had to turn up the volume on the television or miss half the dialogue.

So there I was, along with Michelangelo, having a spider's web in one ear and a cricket singing, not only all night, but all day, in the other.

Inexplicably, there were some days when I felt that the problem had suddenly disappeared, so hardly noticeable was the adventitious sound in either ear. On other days, it was a high-pitched alarm whistle that overlay every sound and made hearing under any circumstance more difficult. I tried to correlate this variation in the intensity of the tinnitus with every available circumstance and situation, all to no avail.

I finally came to explain it as a general phenomenon that I called the "periodicity of well-being." Some days the whole body machinery seems out of kilter—the head, the limbs, the gut—and all other components of the human machine feel unoiled and somewhat awry, not with any specific disorder, but just a general deviation from the norm of "feeling well." It is on these days that the cricket sings the loudest and the spider's web is the thickest. It is also on these days that the joints ache a little more, fatigue occurs earlier, and energy level is at its nadir.

Then there are days when "lo, the lark sings hymns at Heaven's gate." The head is clear, the limbs are supple, the joints are painless, and there is no limit to what can be accomplished. On such days, both the hearing and the tinnitus seem better and hope springs anew that the disorder may have disappeared. This periodicity has no rhythm or definable explanation.

Like most physicians, I deferred seeking further medical attention or advice for my increasingly annoy-

(Morgenstern L: My pets, the spider and the cricket. West J Med 1995; 163:483-484)

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ing affliction. I kept hoping against hope that it was self-limited, that I would awaken one morning to find it gone. I also entertained the feeble hope that it was a labyrinthitis or some other bland inflammatory condition that would play itself out, so I could once again enjoy the luxury of silence.

Then, two occurrences, one close to the other, helped catapult me again into the office of the otolaryngologist. The first of these was my attendance at a Jewish wedding, where the postceremony festivities were presided over by a loud, brassy master of ceremonies leading an equally brassy band blaring forth in megadecibels. The combination of the crowded hall, the constant aural offense of the band, and the incessant chatter of the master of ceremonies set my ears ringing like a thousand church bells, and I strained unsuccessfully to hear what my partners at the dinner table were trying to say. Several times, the ringing became so intense as to be almost painful, causing me to leave the room for some relief. For days thereafter, the intensity of the high-pitched sounds in both ears continued, an unsolicited memento of the raucous wedding.

The second occurrence was a surprise, a physical sensation that I had never before experienced. Several days after the wedding, on a sunny morning while walking with my wife at a leisurely pace, I looked to one side and suddenly felt as if something or somebody had seized me by the shoulder and spun me around clockwise, headlong toward the ground below. In utter amazement, I found myself on the ground, bewildered as to what might have happened. I had not felt faint. My pulse was slow and regular. There was full power in all extremities. The major accompanying symptom as I sat on the ground was apprehension. It was but a single episode that passed quickly, but it was worrisome enough to make me seek medical help again.

The second physician was an old friend, a well-known otologist at the university. He listened carefully to my complaints and ordered the battery of tests usually done to investigate my malady. In addition to the physical examination, there was another audiometry and a test of the tympanic membranes. Both of these failed to reveal any notable abnormality.

Also ordered was a magnetic resonance imaging (MRI) procedure, a new experience for me. With most serious etiologic mechanisms ruled out, I was given the usual reassurance, and resigned myself to living with a new sensation, with little hope of relief, ever.

I began to make observations into what made the condition better and what made it worse. As mentioned, there were periods when it was better for no obvious reason, the periodicity of well-being. It was also made better temporarily if I occluded my ear canals with fingers or cotton, excluding all external sounds. At times, it seemed to me that it was made better if I was at rest rather than engaged in activity. But more than anything else, it was made better by diversion. If I became occupied with some task or thought that claimed my complete attention, I was often surprised that I had not noticed the tinnitus at all. This, then, became my most potent weapon against the unwanted sounds.

Many things made it worse. As mentioned before, loud noises of any kind (especially within a room), inevitably caused a worsening that lingered for some time. At home, the tinnitus was worse in some rooms than in others, having something to do with the configuration of the room. The ringing was also made worse if I spoke loudly at long intervals, the crescendo of adventitious sound building the longer my speaking went on. It was made worse when I was unduly fatigued, when I was under unusual physical exertion, or when I became upset for any reason. It seemed to me that there might be some relation with heightened blood pressure, although I never took my blood pressure on these occasions. At times it seemed to me that it was worse on immediately rising in the morning, diminishing as the day went on. At other times, the ringing grew worse as the day progressed. Those were my "bad ear" days.

As for the episode of vertigo, I had several more minor episodes, but these gradually diminished and eventually disappeared.

I should consider myself fortunate, along with millions of other victims of this annoying malady, inasmuch as I have only the garden variety or most common form of tinnitus. The diagnostic garden is filled with a vast array of exotic disorders, such as neoplasms, aneurysms, unusual inflammations, malformations, and a frighteningly long list of others. They are described in exquisite detail in otologic texts. Some of the varieties are pulsatile, others vibratory. When the etiologic agent is unequivocally discoverable, treatment is perhaps possible. For the vast majority, of which I am one, the cause remains an unfathomable mystery, its sufferers doomed to life without silence.

Few things in nature have an elemental purity, such as sunlight or newly fallen snow, for example. Among them is utter, undiluted, and unsullied silence. What provoked my feeling of panic initially, when the ringing became constant, was that I should never again experience that exquisite luxury of the pure absence of sound.

But as every physician knows, time heals many ailments by its mere passage. Although the ringing has not changed in character and there is a gradual loss of auditory acuity, still, neither is life-threatening. Diversion has remained the most reliable remedy. Another delectable aid is music, which masks, dilutes, and sweetens the unpleasant and unwanted noise.

In short, I have made peace with those two creatures, who at first I deemed implacable enemies. I have made the spider and the cricket my companions for life, my pets. After all, it is the only way we can live together in peace.

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Editorials

A Picture Is Worth a Thousand Words

PICTURE THIS: Charles Dickens is meeting with his editor in a book-lined room. The editor is looking down his nose disapprovingly, saying, "Come, come, Mr Dickens. Either it is the best of times *or* the worst of times." But Dickens was right. It is both.

To be fair, we have more than ever before: more information available; more ways to help. To be honest, medicine is taking a beating. Taking care of patients is harder. Research and education seem to be faltering. This is a time when we need to pull together, working toward resolving conflicts, affirming principles, and strengthening the links between science, education, and the public. Physicians are the binding force.

Medical journals support the profession as part of that binding force. Their purpose is to inform, to inspire, to raise issues and ask questions, to serve as anchors and boosters. They are the product of devoted effort by many: authors, reviewers, staff members, editors. Because of falling advertising revenue and increasing competition from electronic and popular media and despite economies of desktop publishing and other ways of increasing productivity, the future of medical journals is being questioned. As THE WESTERN JOURNAL OF MEDICINE nears its centennial, we are acutely concerned about its immediate future. Will short-term problems cancel long-term triumphs?

Where does the *Journal* stand? What are we trying to do? What do people say about it? The *Journal*, along with *Annals of Internal Medicine*, *JAMA*, and *The New England Journal of Medicine*, is one of four members in the United States of the Vancouver Group (the International Committee of Medical Journal Editors). The *Journal* has over 43,000 readers across the country and around the world, making it one of the largest peer-reviewed journals. It bridges the entire spectrum of medical practice. It serves a unique function as a forum for medical perspectives in the western United States. It tries to be in the forefront of presenting creative, scientific thought while addressing issues affecting the practice of medicine. Our friends tell us that the *Journal* is a widely respected, reliable, and readable source of practical information for clinicians, both generalists and specialists. Not willing to rest on our laurels, we have plans for the Internet and for book publishing. But, despite accomplishments (and never claiming perfection), the *Journal*'s future is under particular threat. Budgetary and other constraints are calling into question the *Journal*'s continued existence.

Picture this: Priorities swerve away from science and education, away from advocacy for patients and knowledge. Doctor-patient relationships wither; trust wanes. The profession would look like the specters from Dickens's *A Christmas Carol.*

How can we avoid this nightmare? Physicians need to develop a full, robust, vibrant renewal. We need to act on shared values. Right now, we all need to support one another and whatever we have, including THE WESTERN JOURNAL OF MEDICINE, that binds us together, in words and pictures, as a profession. We welcome your comments.

LINDA HAWES CLEVER, MD

Chemical Messengers of the Gut

EARLY INVESTIGATIONS of Pavlov detailed how motility and secretion of the gastrointestinal tract were regulated by the nervous system. Elegant descriptions of the cephalic phase of gastric secretion highlighted the importance of neural innervation to the stomach and intestine. During these studies, however, it was also observed that despite cephalic stimulation, little was secreted from the pancreas until acid chyme actually reached the duodenum. This observation was the spark that prompted Bayliss and Starling in 1902 to investigate how the peripheral nervous system might control this intestinal function. Instead, what they discovered was the first hormone. C. J. Martin, Director of the Lister Institute (Middlesex, England), described it thus[1(p902)]:

> I happened to be present at their discovery. In an anesthetized dog, a loop of jejunum was tied at both ends and the nerves supplying it dissected out and divided so that it was connected with the rest of the body only by its blood vessels. On the introduction of some weak HCl into the duodenum, secretion from the pancreas occurred and continued for some minutes. After this had subsided, a few cubic centimeters of acid were introduced into the (de)nervated loop of jejunum. To our surprise, a similarly marked secretion was produced. I remember Starling saying that "it must be a chemical reflex." Rapidly, cutting off a further piece of jejunum, he rubbed its mucous membrane with sand and weak HCl, filtered [it], and injected it into the jugular vein of the animal. After a few moments, the pancreas responded by a much greater secretion than had occurred before. It was a great afternoon.

The substance discovered was named secretin for its ability to stimulate pancreatic juice secretion. The excitement of the discovery is conveyed in this message, although it is unlikely that the investigators realized that their experiments would give birth to an entirely new discipline in physiology, namely endocrinology. Ernest Starling proposed the name "hormones," or chemical messengers, for all such active principals formed in one part of the body and distributed by the circulation to excite the normal functioning or stimulate growth of other parts. This concept revolutionized biologists' understanding of how interrelated gastrointestinal processes could be coordinated by chemical messengers. From that time, research emphasis on neural control of the gut moved to the investigation of hormone transmitters.

As improved methods have been developed for extracting, purifying, and sequencing gastrointestinal hormones, the discovery of peptides exceeded the capability of physiologists to establish their biologic functions in the whole organism. One difficulty in studying gastrointestinal hormones has been the lack of organs, or tissues, with a uniform or high concentration of endocrine cells.

Typically, hormone-secreting cells of the intestine are isolated cells scattered throughout the mucosa. As depicted by Yee and Mulvihill elsewhere in this issue of the journal,[2] hormone-producing cells not only may secrete their transmitters into the bloodstream, but they may act locally through paracrine or autocrine pathways. Although the cellular distribution has provided substantial obstacles for investigators, teleologically this design enables peptide-secreting cells of the gastrointestinal tract to exert both nearby effects, by achieving high concentrations of peptide in the surrounding extracellular environment to regulate nearby cells, and more global effects on distant target tissues as they are transported by the circulation.

To circumvent problems in studying the cellular regulation of gastrointestinal hormone secretion, methods have been developed to enrich cells using elutriation or fluorescence-activated cell sorting. Also, intestinal cell lines and transgenic mouse models are used to explore the regulators of hormone secretion and the pathophysiologic consequences of excess hormone production or hormone deficiency. When combined with organ and tissue preparations and the ability to study brain-gut interactions in whole animals, the relationship between chemical transmitters as hormones and their roles as neurotransmitters can now be better appreciated. It is striking that many peptides originally discovered in the intestine, such as cholecystokinin and substance P, have important physiologic roles in the brain and nervous system. Therefore, some transmitters are produced by endocrine cells of the intestine while the identical peptides can exist in neurons innervating the gut or other organs where they serve as neurotransmitters. Some would interpret the ingenuity of using the same peptide for distinct actions in the gut or brain as evolutionary conservation.

Yee and Mulvihill have provided illuminating examples of the interrelation of peptide transmitters and neural regulation of the gastrointestinal tract. The complementary roles of vasoactive intestinal peptide (VIP) and nitric oxide in esophageal motility and lower esophageal sphincter relaxation enable us to appreciate the pathophysiologic state that produces achalasia when these neurons are lacking. Analogies are drawn to Hirschsprung's disease, where colonic obstruction results from an aganglionic segment involving the internal anal sphincter. This defect in the enteric nervous system results in a deficiency in VIP- and nitric oxide-containing neurons innervating the gut. The authors provide intriguing evidence that peptide transmitters also may be involved in the pathogenesis of other diseases not normally thought of as neuroendocrinopathies of the gastrointestinal tract, such as hypertrophic pyloric stenosis, scleroderma, and inflammatory bowel disease. It is speculated that even irritable bowel syndrome has a hormonal component.

The physiology of several enteric hormones has been elucidated by nature's accidents, whereby a tumor may secrete excess hormone in an unregulated manner. In patients with gastrinoma, gastrin not only causes perilous gastric acid hypersecretion, but also has profound trophic effects on the gastric mucosa.

Although somatostatin inhibits the secretion of most hormones, patients with somatostatin-secreting tumors suffer from diabetes mellitus, providing insight into the relative contribution of somatostatin in the regulation of insulin and glucagon secretion. Other manifestations of somatostatin-secreting tumors such as steatorrhea and gallstones indicate that enteric hormones are critical regulators of normal gastrointestinal function.

Finally, the genetic causes of familial endocrine diseases are within sight of medical geneticists. With the recent identification of the gene responsible for multiple endocrine neoplasia (MEN) type 2,[3,4] the genetic basis for MEN-1 and its associated features of hormone-secreting tumors of the pancreas should provide additional insight into the regulation of gastrointestinal endocrine cell secretion, growth, and neoplasia.

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Correspondence

Patients From Japan and Physician-Patient Communication

To the Editor: As a physician whose practice includes a considerable number of patients from Japan, I must comment on the article by Dr Asai in the July issue.[1] Asai assumes that the public perception (at least in Japan) is that a diagnosis of cancer leads to certain death. In fact, nothing is further from the truth; as is commonly known, certain "cancers" can take chronic courses. It is more important to dispel the "cancer equals death" myth than it is to dwell on telling or not telling the truth. It is not the "cancer" diagnosis but rather the hopelessness that the word connotes that is potentially harmful to patients.

The physician-patient relationship, by definition, can never be an equal partnership, as the author states. Each party brings to the table different points of view. To conclude from this that patients are unwilling, incapable, and even undeserving of knowing the truth about their diagnosis is paternalistic and patronizing. Further, the questionnaire that the author proposes is designed to collect data in the premorbid state. The physician-patient relationship (as with any relationship) is dynamic. What patients' wishes were when they were asymptomatic and robust are certain to differ from their wishes in the terminal stages of pain, cachexia, and stupor.

Every health care professional realizes the importance of patient compliance in treating any medical condition. The rising cost of medical care can be controlled only when all parties are willing to cooperate. Also, certain cancers invite metachronous lesions that require future surveillance. For these reasons, telling patients the truth is an important public health measure.

The "truth tellers" and the "truth withholders" have long waged a debate, especially in Japan. The truth tellers have steadily gained in strength and in numbers. With reform of the liability laws on the horizon in Japan, the question will soon become moot, as it became decades ago in this country. Asai's article is outdated.

With Japanese patients in my practice, I exercise the same compassion and empathy that I extend to other patients. When they are in the denial stage, I respect their wishes; at the same time, I help them into the anger and acceptance stages that inevitably follow. I also remind myself that I practice in California, where I am held to the highest standards in the world.

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* * *

Dr Asai Responds

To the Editor: As Dr Uyeda rightly points out, my article and the questionnaire are outdated for most physicians and patients in the United States, where complete disclosure of medical information and shared decision making are common and mandated. But this is probably not the case in many other countries. That article was intended for physicians in countries where disclosing a diagnosis of cancer is still controversial. I also wanted to introduce to the readership in the United States the several barriers to truth telling that exist in some countries. An awareness of cross-cultural differences might be useful in dealing with patients from other countries, especially for physicians who live in areas with a large number of immigrants.

I agree that the physician-patient relationship is dynamic and will change and that patients' wishes expressed when they are healthy or asymptomatic may not represent their wishes in the terminal stages of disease. I mentioned in the article that we need to repeat the same questions periodically. Nevertheless, what is now important in Japan is to try to know patients' wishes regarding their medical information and condition, including a diagnosis of cancer, as early as possible.

The physician-patient relationship in Japan is strongly influenced by the opinion of patients' families. Once patients get sick, their family may treat them as if they were incompetent and strongly request the physician in charge not to tell the patients the truth, even if this were against a patient's wishes. Therefore, health care professionals must know their patients' concrete wishes so that families can be persuaded to allow the truth to be told. Only when patients have expressed their wishes in writing is it possible for us to disclose the truth against families' wishes.

Uyeda's method of dealing with his Japanese patients with serious medical problems is appropriate, and physicians practicing in Japan should learn from him. We have to learn how to break bad news to our patients. I suspect, however, that his Japanese patients in the United States have been influenced by American culture. Japanese patients in the United States and those in Japan probably have different attitudes toward medical problems because the two cultures are strikingly different. The relationship between Japanese patients and their families might also differ in the two countries. Even patients in Japan differ from each other, although they are living on an island smaller than California.

I really hope that my article soon becomes outdated in Japan and other countries, although history has proved that old customs die hard.

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Salty Milk—When to Worry

To the Editor: Lance A. Chilton, MD, in his article in the July 1995 issue, says, "The issue of being able to breast-feed once a high sodium level has been detected in the milk has not been addressed."[1(p76)] He then footnotes one of my articles.[2] His conclusion is surprising because, of the 130 mothers in my study, 60 of them had elevated breast-milk sodium (Na^+) levels and continued to breast-feed.

To better understand this issue, the following points, which are discussed in my article, need to be understood. During lactogenesis, the breast-milk Na^+ level drops about 24 hours before the milk volume increases, normally around the third or fourth day.[3] An elevated breast-milk Na^+ level after this time implies delayed or impaired production. It is only with the stimulation of frequent and effective emptying that the paracellular junctions tighten. With this closure, the amount of the plasma-derived products, such as sodium, declines and that of the nutrient products, such as lactose and fat, increases. Primiparous mothers especially are often unaware whether they are nursing effectively and frequently enough to adequately stimulate lactogenesis. Finally, as this study shows, there is a critical window of time in the first week after which the breasts become less responsive despite aggressive efforts to promote frequent and effective emptying. The longer the breast-milk Na^+ level remains elevated, the less likely a woman is to produce enough milk to support her infant.

In the case described by Chilton, most likely the infant was ineffectively nursing and, instead, using the breast as a pacifier. There should have been no concern about malnutrition or cystic fibrosis in this mother, as it has been shown that women with these conditions produce milk with a normal salt content.[4,5]

Chilton also suggests that the breast-milk Na^+ level in this woman's milk was even higher on earlier days, as the Na^+ level normally falls each day after birth. This trend, however, does not occur without frequent and effective emptying from the first day. The 36-hour period between the discontinuation of breast-feeding and the time of milk collection would most likely result in a somewhat higher value on day 9 than on day 7, as abrupt weaning results in a further elevation of breast-milk Na^+ levels.[6] Nonetheless, clearly this woman's milk production was impaired.

Chilton questions whether a 10% weight loss should be of concern and whether there are any sensitive screening indicators of impending problems. Although this was not reported in my article, every infant with a weight loss of 10% or more between the third and eighth days of life had a serum Na^+ level measured before supplementation was initiated. Of the 130 babies, 20 (15.4%) had a weight loss of more than 10%. Of these, 6 (30%) had hypernatremia (defined as a serum Na^+ level of >150 mmol per liter).[7] All six infants had a weight loss of greater than 12%. Of the 20 women, 19 (95%) had elevated breast-milk Na^+ levels (Table 1). All women continued to breast-feed with formula supplementation if indicated by their baby's weight or temperament. Pumping was usually needed to improve effective emptying. No complications from continued breast-feeding were observed, presumably because the higher the Na^+ level, the smaller the amount of breast milk (and the greater the amount of formula) the infant would receive. In cases where production improved substantially, the breast-milk Na^+ level

TABLE 1.—*Infants With Weight Loss of More Than 10% Between Days 3 and 8*

Case	Serum Na^+ Level, mmol/liter	Age, days	Weight Lass, %	Breast-Milk Na^+ Level, mmol/liter*
1	167	6	15.3	62/42
2	159	5	14.8	42/39
3	155	4	15.0	56/42
4	153	6	16.9	62/41
5	152	3	13.9	42/37
6	152	5	12.5	68/51
7	150	5	12.6	35/18
8	150	3	12.2	50/36
9	150	4	11.2	78/73
10	149	5	11.9	20/18
11	147	6	10.1	14/11†
12	147	3	11.3	62/51
13	146	3	10.9	60/47
14	145	5	12.1	26/22
15	145	5	13.0	58/68
16	144	5	10.5	19/16
17	144	4	14.8	32/31
18	143	5	10.0	25/22
19	143	7	10.9	21/23
20	142	8	11.2	32/15

*Right/left breasts
†Normal values.

would first drop. This level is a sensitive indicator of impaired lactogenesis and, in combination with a weight loss of more than 12%, should alert us to consider hypernatremia in an infant.

From experience, I would concur that the woman in Chilton's case was producing only scant volumes of breast milk and would not have eventually succeeded in exclusively breast-feeding. It seems most reasonable in this case to withhold feedings entirely until the severe hypernatremia is corrected. In my study, many women who failed to exclusively breast-feed their first infant succeeded with their next baby.

Physicians need to be aware of the implications of an elevated breast-milk Na^+ level and to support women in their efforts to augment their production if lactogenesis is impaired.

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* * *

Dr Chilton Responds

To the Editor: I appreciate Dr Morton's letter and her further explication of her excellent article. I wish it had been available to me when I was caring for the child described in my case report. Morton makes a number of important points: There is a critical period for the establishment of breast-feeding. After that time, it is unlikely that it will become effective. The breast-milk Na^+ level is a marker for the adequacy of the breast-milk supply. A weight loss of greater than 12%, especially if combined with an elevated breast-milk Na^+ level, should alert us to impending breast-feeding failure and infant hypernatremia. With appropriate help, women who have failed to provide breast milk on one occasion can successfully breast-feed subsequent infants.

Our practice has now instituted a two- to three-day follow-up clinic for all women delivering infants at our institution. The now almost universal practice of early hospital discharge of mothers and infants, previously risky especially for breast-feeding dyads, provides the impetus for this early visit. We take that opportunity to check each infant's weight, assess for jaundice, and answer parents' questions in a group session. This allows each parent to hear the questions posed by others, as well as the answers to the questions, and it allows us to be certain that breast-feeding remains the positive influence on each family's life that we expect it to be.

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Lessons From the Practice

Rounds

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We met in the team room—two second-year residents, two interns, and two third-year medical students, all men. Jeff presented the case, and Andy acted as scribe, making notes on the board. Every few minutes, I would interrupt and ask questions of the group. As the case unfolded, we talked about points of the history and physical and what tests might be useful, developed priorities of management, and weighed the likelihood of various diagnoses.

Jeff described the case of a woman in her 60s who had come to the hospital because of severe dyspnea, cough, and an abnormal chest x-ray film, referred from a community hospital after treatment of presumed pneumonia failed to produce a response. Twenty years ago the patient was diagnosed with sarcoidosis that presented as hilar adenopathy. This had resolved after a short course of prednisone. She had been a smoker but had stopped four years ago. Over the past three weeks, increasing dyspnea and cough had developed. The cough was so frequent and severe that her chest hurt. The day before admission, she had coughed up some blood. She had noticed some swelling of her face and neck.

We talked about the differential diagnosis. Sarcoid was strongly considered, and pneumonia was also high on the list. The facial and neck swelling raised the possibility of superior vena cava syndrome, constrictive pericarditis, or pericardial effusion. Cancer was also possible, given her smoking history and bloody cough. A chest radiograph was reviewed. There was bilateral hilar adenopathy, but the densities extended superiorly on both sides, compressing the left main-stem bronchus and impinging on the lower third of the trachea. The heart looked a little enlarged, and the paratracheal zone was full. The x-ray film findings certainly added a sense of urgency to the diagnosis. It was clear that she was ill and that a diagnostic procedure needed to be done. Because she was not febrile, her blood pressure was normal, and no deterioration was evident over the past six hours, a thorough discussion of diagnostic tests was in order.

The group firmly focused itself on these issues. How to get to her disease was the question. Bronchoscopy? Mediastinoscopy? Would endotracheal intubation be necessary, or would it be hazardous in this patient? Would split ventilation be necessary? How about an open lung biopsy? Or should we just get an ACE [angiotensin-converting enzyme] level?

We had used 40 minutes of our hour and were eager to get to the bedside. As we walked toward the patient's room, I exchanged a few more points with the students—the physiology of a pulsus paradoxicus, alveolar-arterial gradients, the urgency of the situation. Jeff secured permission for us to see her as a group, and we went in. I introduced myself and the half of the team she had not yet met. Her husband stood protectively nearby.

The first thing we noticed was her puffy neck and face. She lay in bed quietly, but the rising and falling of her chest were clearly visible. She could barely complete her brief greeting. Her voice was strained, and she coughed once. I told her that we were making teaching rounds and had been talking about her and wanted to meet her to learn more about her difficult illness. I asked how she was feeling.

She looked at me, and then her eyes filled with tears as she said, half sobbing and gasping,

> I can't tell you how distressed I am. I've been here since last night, and I told them I needed something for the cough. It took them 8 hours to get it to me from the time I first came to the hospital. Do you know how terrible it is to, well, have an accident, each time you cough? It is so embarrassing. I'm so exhausted from coughing all night. I told them, but nobody helped. This is so difficult for me, especially a woman with all you men, but I have to tell you what this is like for me. And no one has told me what is going to happen—I thought I was going to have a test today. I haven't eaten anything all day. I get different stories from different doctors. I don't even know who's really my doctor.

She was distraught. She sobbed, then fought for self-control.

I told her in as supportive a way as I could that I understood her distress and that she had obviously not been given relief from what had been bothering her most—her cough-induced incontinence. We talked a bit about the unfortunate fact of one physician admitting her and then another assuming care in the morning. We talked about the difficulty of determining the safest course for diagnosis. I noted that many consultants would see her and that it was ultimately in her best interests to have as complete an evaluation as possible. But also I said that I understood the bewildering experience of being in this setting, sleep-deprived, uncomfortable, and embarrassed at making herself wet.

She looked greatly relieved to have expressed herself. I wondered what had enabled her to speak up so well. I was glad she had, for we had had an emotional discussion. I was glad that the house staff and students

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had witnessed this extraordinary disconnection and reconnection. We had gone from discussing biomedicine in the classroom to the bedside where an entirely different dimension of doctoring had become apparent.

After that, I asked her if I could demonstrate some physical findings. We looked at her central venous pressure, for a Kussmaul sign and for a Pemberton sign. We looked at the distended veins in her chest. No doubt about it, she had superior vena cava syndrome. The only question that remained was why. We said goodbye and thanked her again for sharing with us. Outside her room, we talked briefly about the meaningfulness of this encounter for all of us.

The next day I visited the patient again, this time alone. She felt pretty good now that a plan had been formed. She was having a mediastinoscopy in the afternoon. She expressed gratitude at the support everyone had given her, the nurses and doctors. She asked me to come again.

I did come again, two days later. She had small-cell lung cancer. The patient was tearful but upbeat. She had begun taking prednisone, had had her first dose of chemotherapy, and felt pretty good. She smiled bravely and said, "I am a survivor, and I'll do just fine." Her arm was warm where I placed my hand, letting it rest there briefly. I would see her again.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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Topics in Primary Care Medicine

Congenital Heart Disease in Adults

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Patients reaching adulthood with unoperated and operated congenital heart disease require attention to issues of exercise, antibiotic prophylaxis, contraception, and pregnancy. A careful clinical history is important to establish the degree of a person's disability, if any, and the symptoms responsible for the disability, whether due to heart failure, cyanosis, or both. The findings of a physical examination and a noninvasive evaluation, including electrocardiogram, chest x-ray film, and echocardiography, are often sufficient to establish a diagnosis and to assess the adequacy of a previous operation. Transesophageal echocardiography and magnetic resonance imaging are adjunctive procedures that are indicated when routine transthoracic echocardiography is limited. Cardiac catheterization may be necessary when the noninvasive data are ambiguous and to assess coronary artery disease (congenital and acquired) in patients considered for surgical therapy. Cardiac catheterization is increasingly therapeutic (such as percutaneous pulmonary balloon valvuloplasty) as well as diagnostic. Primary surgical repair or additional surgical palliative procedures should be considered in symptomatic adults. A patient with Eisenmenger's syndrome—severe pulmonary hypertension—is a special case that may be amenable only to transplantation.

(Foster E: Congenital heart disease in adults. West J Med 1995; 163:492-498)

About 500,000 patients in the United States alone have survived into adulthood with congenital heart disease, with about 20,000 additional patients reaching adulthood each year.[1,2] These patients have been classified as follows: those with natural survival, those with surgical correction, and those who have had surgical palliation.[3,4] Patients in each category require guidance on issues regarding exercise prescriptions, childbearing, anticoagulation, and antibiotic prophylaxis. In addition to the medical consequences of their disease, they face issues concerning insurability and disability.

As adults, they may present to a primary care physician as asymptomatic persons who are "reentering" the health care system as a result of joining a health maintenance organization or of pregnancy, either anticipated or established. On the other hand, they may have "turned 21" and thus are referred by their pediatrician or pediatric cardiologist. Although a primary diagnosis may have been made in childhood, the original diagnosis is not necessarily correct. Improved noninvasive and invasive imaging methods may establish the presence of an entirely different lesion. Alternatively, the primary disorder (such as coarctation of the aorta) may have been correctly diagnosed and may be adequately treated, but a second lesion (for instance, bicuspid aortic valve) may have become clinically manifest. A previous palliative operation may present with "late" failure, such as recoarctation or that due to degeneration of a bioprosthetic valve. In some cases, surgical and nonsurgical therapeutic interventions have evolved such that previously "untreatable" disease (such as pulmonary atresia) is now frequently amenable to repair.

Clinical Assessment of Adults With Congenital Heart Disease

History

Especially critical to the care of these patients is compulsive information gathering. Reports must be obtained from previous catheterizations, echocardiographic studies, and other noninvasive imaging such as nuclear shunt studies and magnetic resonance imaging. Operative reports should be reviewed to determine the precise procedure done and the surgeon's assessment of the adequacy of repair.

In taking a patient's clinical history, it is important to establish the degree of disability, if any, and the symptoms responsible for the disability. The following questions are important to address: Are there symptoms of heart failure? If so, do they manifest as dyspnea due to pulmonary congestion or fatigue due to low output? Has the patient noted increasing cyanosis? If so, how long has the change been noted? The review of systems needs to address the extracardiac manifestations of this disease, especially in patients with cyanosis. Headaches and visual symptoms may be due to severe polycythemia in a patient needing phlebotomy or to iron deficiency in a patient with an excessive number of phlebotomies. Gout and renolithiasis may result from hyperuricemia. Frequent pulmonary infections may be a manifestation of

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an uncorrected atrial septal defect. Hemoptysis resulting from pulmonary hemorrhage may be life-threatening in a patient with irreversible pulmonary vascular disease due to an uncorrected ventricular septal defect or a patent ductus arteriosus—that is, Eisenmenger's syndrome.

Physical Examination

It is beyond the scope of this review to discuss the myriad physical findings in congenital heart disease except in the broadest terms. Interested readers are referred to several excellent sources for this information.[5,6]

The presence of cyanosis and clubbing should be noted, and if present, all four extremities should be examined. Differential cyanosis that spares the upper extremities and involves the lower signals the presence of a patent ductus arteriosus with right-to-left shunting. These physical findings can be confirmed noninvasively using pulse oximetry. Chest wall deformities (pectus excavatum) and other physical stigmata (webbed neck, stature) may be signs of congenitally inherited syndromes such as the Marfan, Noonan, or Down syndromes. Pulses should be examined; a radiofemoral pulse delay is evidence of aortic coarctation. Jugular venous distention suggests the presence of systemic venous congestion, possibly due to heart failure. The precordium should be inspected and palpated for evidence of ventricular enlargement and the presence of a thrill.

Careful auscultation is crucial, with attention to the following: the intensity of S_1; the presence of systolic clicks; the splitting of S_2; systolic, diastolic, and continuous murmurs and their location and radiation; and gallop rhythm. A systolic ejection click may be due to either aortic or pulmonic stenosis, whereas a midsystolic click suggests mitral valve prolapse. Multiple systolic clicks with a systolic murmur at the right sternal border are usually associated with Ebstein's anomaly—a rare condition in which the septal leaflet of the tricuspid valve is deformed and displaced apically. A single S_2 is present in severe aortic stenosis (P_2 only) or pulmonic stenosis (A_2 only). A fixed, widely split S_2 is strongly suggestive of an atrial septal defect.

Although a machinelike, continuous murmur may be due to a patent ductus arteriosus, continuous murmurs are also heard in patients who have had palliative systemic-pulmonary shunts or who have native aortopulmonary collaterals. An early diastolic blowing murmur of pulmonary insufficiency is high pitched in the presence of pulmonary hypertension and low pitched in patients who have had a previous operation for pulmonary valve stenosis with normal pulmonary pressure. Paradoxically, the murmur of a ventricular septal defect may be loud and associated with a thrill if the defect is small and absent or soft if the defect is large and associated with pulmonary vascular disease (Eisenmenger's syndrome). Thus, the best-informed examiner will be able to glean the most information from the physical examination.

Chest X-ray Films

Many congenital cardiac abnormalities are associated with cardiac malposition; thus, the heart may be in the left chest (levocardia), right chest (dextrocardia), or in the midline (mesocardia). The position of the stomach bubble should also be noted for situs inversus (right-sided). In these cases, the right-sided main-stem bronchus will be longer. Among the other important radiographic findings are evidence of cardiomegaly, specific chamber enlargement, right or left aortic arch, and pulmonary artery dilatation. As in acquired heart disease, interstitial edema with Kerley B lines is obviously a sign of left-sided heart failure, but a plethora of the peripheral vessels in association with dilated proximal pulmonary vessels suggests a large left-to-right shunt. If the peripheral vessels appear "pruned" in the presence of dilated main pulmonary arteries, severe pulmonary vascular disease is likely to be present. "Notching" of the lower borders of the ribs due to the impingement of large collateral vessels is a pathognomonic sign of aortic coarctation.

Even before further noninvasive testing is done, the history, physical examination, and chest x-ray film provide clues as to the diagnosis and the condition of an adult with congenital heart disease.

Electrocardiogram

The electrocardiogram is almost always abnormal in patients with congenital heart disease. Although the abnormal findings may not be specific to a patient's lesions, they provide important clues to the diagnosis. Rhythm disturbances are common. Atrial and ventricular tachyarrhythmias are seen, and both may presage sudden death. Atrial flutter and fibrillation are particularly ominous in patients who have had surgical palliative procedures for transposition of the great arteries (Mustard or Senning procedure) and tricuspid atresia (Fontan operation). Ventricular arrhythmias are common following the repair of a tetralogy of Fallot, but fortunately, sudden death is uncommon.[7] Second- and third-degree atrioventricular blocks are most frequently seen in patients with corrected congenital transposition of the great vessels, with complete heart block occurring at a rate of approximately 2% per year in this condition.[4] Right and left atrial enlargement causes the expected P-wave abnormalities. The QRS axis and voltage are determined by the extent of ventricular chamber hypertrophy. An incomplete right bundle branch block is present in about 95% of patients with atrial septal defects; the QRS axis depends on the location of the atrial septal defect. In the most common type, an ostium secundum defect located in the region of the fossa ovalis, the axis is vertical or rightward. The ostium primum defect, located in the lower portion of the interatrial septum and frequently seen in patients with the Down syndrome, is associated with a superior axis—that is, left anterior hemiblock. A tall R wave in the right atrial precordium (lead V_1) with deep S waves in the left precordial leads (V_6) suggests elevated right ventricular pressures as in pulmonary

stenosis or Eisenmenger's syndrome. Increased QRS voltage consistent with left ventricular hypertrophy can be associated with congenital aortic stenosis or residual hypertension following the late repair of a coarctation.

Finally, although ST and T-wave abnormalities are most often due to the strain associated with right or left ventricular hypertrophy, the possibility of coexistent coronary artery disease should not be overlooked.

Referral for Specialized Testing

The key issue in referring patients with congenital heart disease for further diagnostic evaluation is the experience of the personnel in the facility.

Echocardiography

The sonographer and attending cardiologists in an echocardiography laboratory need to be versed in the anatomy and flow disturbances of the numerous congenital heart defects.[8] A cardiologist should be available for additional procedures, such as administering a contrast medium to detect shunts and to ensure that coexistent lesions are not overlooked—for instance, coarctation in patients with bicuspid aortic valves. The imaging planes available with transthoracic (that is, surface) echocardiography may be limited in an adult, and transesophageal examinations may be required to completely evaluate the cardiac anatomy. Surface imaging, however, remains essential for measuring valve gradients (Figure 1), estimating pulmonary artery pressure (Figure 2), and evaluating chamber hypertrophy and enlargement. The strengths of transesophageal echocardiography are in the evaluation of posterior cardiac structures—specifically, the atria, interatrial septum, pulmonary veins, and the mitral valve. Examples of interatrial septal defects on transesophageal echocardiography are shown in Figures 3, 4, and 5. Another aim of transthoracic and transesophageal echocardiography is to visualize and demonstrate patency of palliative shunts created surgically to improve pulmonary blood flow in patients with cyanotic congenital heart disease.

Doppler echocardiography, performed in association with supine bicycle ergometry, can provide important hemodynamic information during exercise that may help to explain symptoms when resting hemodynamics are ambiguous.[9]

Nuclear and Magnetic Resonance Imaging

First-pass radionuclide studies can be used to estimate the magnitude of a left-to-right intracardiac shunt. Technetium-labeled erythrocytes are administered, and count intensity is sampled at a site over the lung field. An initial increase in counts is seen on the first pass, followed by an early secondary rise due to shunting across the intracardiac defect, with reappearance in the pulmonary circulation. The area under these curves can be derived to measure the ratio of pulmonary-to-systemic blood flow (Q_p:Q_s).

Magnetic resonance imaging is an adjunct to echocardiography in most patients with congenital heart disease.[10] In our experience, it is most helpful in evaluating the great vessel anatomy. For example, the presence and size of the main pulmonary arteries may be an important surgical consideration in determining eligibility for repair in certain patients. Magnetic resonance imaging provides excellent visualization of abnormalities of the aortic arch and descending aorta in patients with aortic coarctation, either untreated or treated.

Cardiac Catheterization

Diagnostic catheterization should be carefully planned following complete review of the clinical and noninvasive data. In fact, many patients can undergo surgical intervention without an invasive study. These include patients with isolated atrial septal defects, mitral regurgitation, and congenitally abnormal (bicuspid) aortic valves. Catheterization is essential when noninvasive data are incomplete to determine the presence and extent of pulmonary vascular disease; evaluate conduit gradients; define collateral circulation to the pulmonary arteries; document the presence of coronary artery anomalies, atherosclerotic coronary artery disease, or both; and to quantify left-to-right shunts when noninvasive data suggest a "borderline" value (Q_p:$Q_s \leq 1.5$:1).

As in coronary artery disease, cardiac catheterization has increasingly become a therapeutic modality in congenital heart disease.[11] The era of therapeutic catheterization began with the Rashkind procedure, a balloon atrial septostomy to improve saturation in newborns with transposition of the great vessels, and it has evolved to include not only aortic and pulmonary valvuloplasty but also more complex procedures such as coil embolization of collateral vessels in pulmonary atresia.[11]

A small-to-moderate patent ductus arteriosus can also be closed using a device, and this may be preferred to ligation and division in an adult.[12,13] Under investigation are devices for the percutaneous closure of atrial and ventricular septal defects. The future availability of nonsurgical therapy may encourage the closure of smaller defects than normally considered for surgical therapy (that is, Q_p:$Q_s \leq 1.5$:1) to prevent the complications of paradoxical embolization and endocarditis.

Prognosis in Patients With Commonly Seen Unoperated and Operated Congenital Heart Defects

Bicuspid ('Congenitally Abnormal') Aortic Valve

The natural history of aortic stenosis presenting in childhood depends on the severity of the stenosis at the time of diagnosis.[14] Once symptoms of aortic stenosis develop, the prognosis without valve replacement is poor, with a five-year mortality approaching 90%. Both percutaneous valvuloplasty and surgical repair (as opposed to replacement) of the aortic valve have had limited success. The rate of reoperation in patients who had initial surgical valvotomy in childhood is high (30%), and the overall 25-year survival rate is about 85%.[14] Thus, aortic valve prosthetic replacement is gen-

Figure 1.—Continuous-wave Doppler flow signal across a stenotic pulmonary valve is obtained from transthoracic echocardiography. The peak flow velocity of 6 m per seconds corresponds to a severe gradient of 144 mm of mercury, which was confirmed at cardiac catheterization.

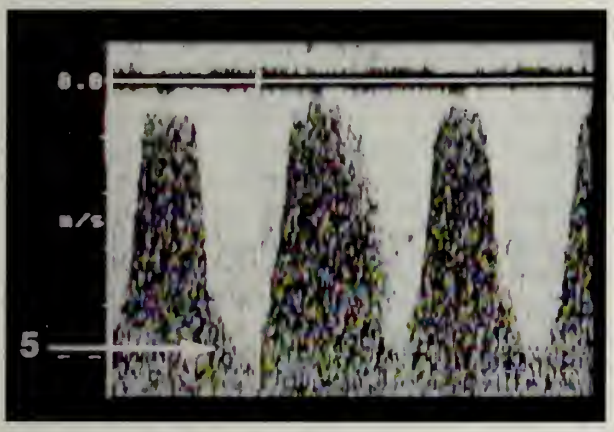

Figure 2.—A continuous-wave Doppler flow signal of tricuspid regurgitation is obtained from transthoracic echocardiography in a patient with severe pulmonary hypertension due to a ventricular septal defect. The peak flow velocity of 5 m per seconds corresponds to an estimated pulmonary artery systolic pressure of 100 mm of mercury.

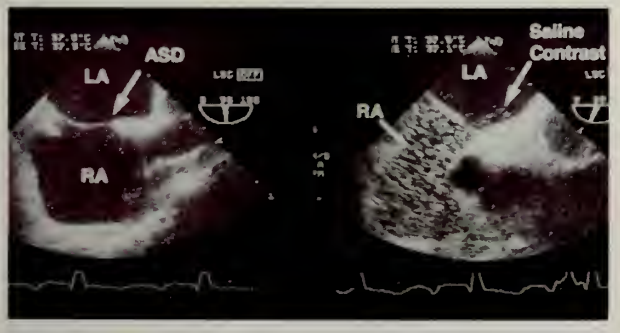

Figure 3.—A small interatrial septal defect **(ASD)** is visualized on transesophageal echocardiography **(left panel).** The defect is in the thin portion of the interatrial septum **(arrow)** between the left atrium **(LA)** and right atrium **(RA). Right panel,** There is evidence of right-to-left shunting during a Valsalva maneuver, with agitated saline solution administered to an arm vein appearing first in the RA, then crossing the defect into the LA **(arrow).**

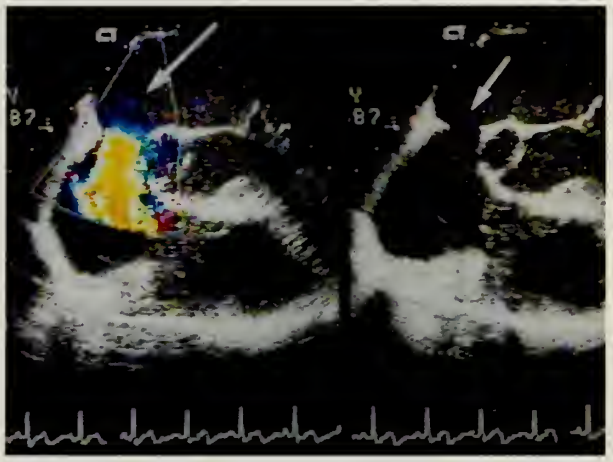

Figure 4.—Right, A large secundum-type interatrial septal defect is visualized **(arrow)** on transesophageal echocardiography. **Left,** Color-flow Doppler demonstrates left-to-right shunting across an atrial septal defect **(arrow).**

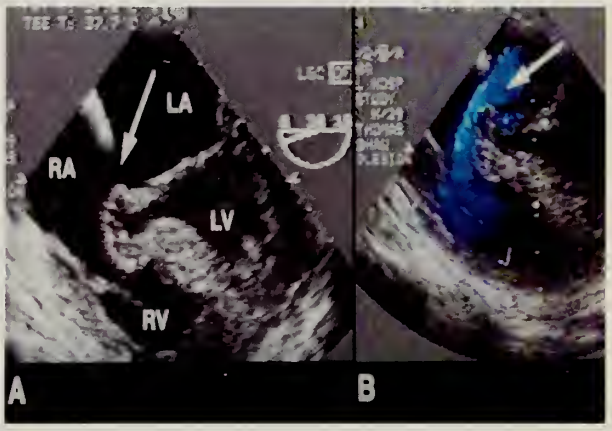

Figure 5.—A, A large primum-type interatrial septal defect **(arrow)** is shown on transesophageal echocardiography. **B,** Color-flow Doppler demonstrates left-to-right shunting across the defect **(arrow).** LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle

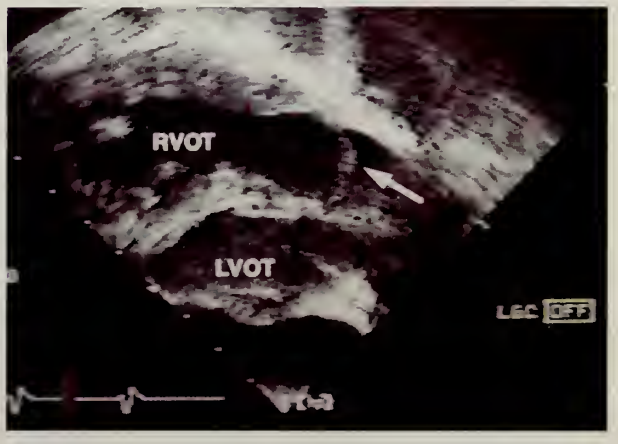

Figure 6.—A severely stenotic pulmonary valve **(arrow)** shows systolic doming on this transesophageal echocardiogram. RVOT = right ventricular outflow tract, LVOT = left ventricular outflow tract

erally necessary in adults. A mechanical prosthesis is more durable than currently available bioprostheses, and the long-term performance of homografts remains uncertain. Unless there are overwhelming contraindications to anticoagulant therapy (such as a young woman contemplating pregnancy), a mechanical prosthesis should be considered.

Pulmonary Valve Stenosis

Although the average life expectancy for patients with severe untreated pulmonary valve stenosis is about 30 years,[5] the natural history of medically treated mild or moderate pulmonary stenosis and surgically treated severe (gradient ≥ 80 mm of mercury) stenosis is excellent, with a 25-year survival of 95%.[15,16] Most patients with valvular pulmonary stenosis are now treated with percutaneous balloon valvuloplasty, which has largely replaced surgical valvuloplasty.[3] Unlike in adult patients with congenital aortic stenosis, percutaneous balloon valvuloplasty appears to be the treatment of choice in adults with pulmonic valve stenosis.

Atrial Septal Defect

Although an unoperated ostium secundum atrial septal defect permits survival into adulthood, the life expectancy is shortened, with only 50% surviving to age 40 and a subsequent mortality of about 6% per year.[4] Although most adults with atrial septal defects have mild to moderate pulmonary hypertension, the late development of severe pulmonary hypertension in older adults appears to be rare (<10%). Another possible complication of interatrial septal defect (even the smallest patent foramen ovale) in adult patients is paradoxical embolization.

Ostium secundum atrial septal defects have been successfully repaired for more than 30 years, with substantial improvement in long-term survival.[16,17] Despite poorer surgical results in older adults (older than 40 years), surgical therapy is probably superior to medical therapy and is recommended in patients with predominant left-to-right shunts (Q_p:Q_s > 1.5 to 2:1) and a low pulmonary vascular resistance. A late operation usually improves the functional class and eliminates the risk of paradoxical embolization, but does not reduce the incidence of atrial arrhythmias. Endocarditis prophylaxis is recommended only during the first six months after the operation.[18] Anticipated technical advances in devices for percutaneous closure may lead to future recommendations for repair at lower shunt ratios to prevent paradoxical embolization.

Interventricular Septal Defects

It is relatively uncommon to see adults with ventricular septal defects because large defects, presenting in infants with congestive heart failure, are usually surgically closed, whereas many smaller defects spontaneously close before adulthood. Severe pulmonary hypertension (Eisenmenger's complex) is more frequent in adults with large uncorrected ventricular septal defects than in those with atrial septal defects. In a series of 67 patients with an uncorrected ventricular septal defect (mean age of 33 ± 11 years), the overall ten-year survival after the initial presentation was 76% and was adversely affected by a functional class of greater than 1, cardiomegaly, and elevated pulmonary artery pressure (>50 mm of mercury).[19] Indications for surgical therapy include a left-to-right shunt of greater than 2:1, recurrent endocarditis, and progressive aortic insufficiency. Patients with severe pulmonary vascular disease are not candidates for ventricular septal defect closure, although they may be considered for heart and lung transplantation.

Ventricular septal defects have been closed surgically for more than 30 years.[16,20] In the earlier surgical era, there was about a 20% incidence of residual left-to-right shunt with a persistent risk of endocarditis. In a recently published, multicenter natural history study, however, second operations were required in only 26 of 468 (5.5%) patients who had their ventricular septal defect surgically closed.[21] The risk of sudden death and complete heart block in patients with a previous repair is low.[22] In summary, most patients who have had a ventricular septal defect repaired in childhood survive to lead normal adult lives.

Tetralogy of Fallot

Tetralogy of Fallot is the most common form of cyanotic heart disease seen in adult patients. The primary lesions in tetralogy of Fallot are ventricular septal defect and pulmonary stenosis; an overriding aorta and right ventricular hypertrophy are, in essence, secondary lesions. The predominant pathophysiology is right-to-left shunting across the ventricular septal defect due to elevated right ventricular pressures resulting in cyanosis. Survival without palliative surgical intervention is uncommon (about 10%) beyond the age of 20 and rare (3%) beyond the age of 40.[4] Unlike patients who have isolated large ventricular septal defects, patients with tetralogy of Fallot are "protected" by pulmonary stenosis from the development of pulmonary hypertension, and they are often surgical candidates as adults.[23] Endocarditis is common in patients with unrepaired tetralogy of Fallot.

Intracardiac repair with closure of the ventricular septal defect and correction of the pulmonary or infundibular stenosis is considered one of the most successful operations in congenital heart disease, leading to the relief of cyanosis. Patients whose tetralogy of Fallot has been repaired may have substantial postoperative sequelae, however, including residual outflow obstruction, pulmonary valve regurgitation, right ventricular aneurysms, and ventricular septal defect patch leak.[24] In a series from the Mayo Clinic (Rochester, Minnesota), 10% of patients required reoperation for these complications at a mean follow-up period of nine years.[25] The incidence of late (older than 25 years) cardiac death in the Oregon registry was 5%, about half of the deaths sudden, presumably due to arrhythmia.[16] Current trends in surgical techniques may reduce the need for reoperation and the incidence of late arrhythmias.[23,24]

Palliative Surgical Procedures for Cyanotic Congenital Heart Disease

The terminology for the surgical procedures used to palliate cyanotic congenital heart disease is littered with eponyms that contribute to the confusion in this area. When cyanosis is on the basis of diminished pulmonary blood flow, palliative procedures have aimed at increasing pulmonary blood flow by directly or indirectly shunting blood from either the systemic venous or systemic arterial circulation to the pulmonary arteries. These procedures have evolved with time as complications became apparent.

The Fontan procedure bypasses the right ventricle by connecting the right atrium directly to the pulmonary artery circulation, separating the systemic and pulmonary venous return. Complications have included arrhythmias, systemic venous hypertension with fluid retention, protein-losing enteropathy (10%), and congestive heart failure.[26] The Glenn shunt (superior vena cava to right pulmonary artery) can be used when a Fontan procedure is contraindicated due to pulmonary hypertension.[3]

Early surgical systemic-to-pulmonary shunts such as the Waterston (ascending aorta to pulmonary artery) and Potts (descending aorta to pulmonary artery) shunts are no longer employed because of the high frequency of pulmonary hypertension.[3] Yet, many patients have survived into adulthood with these procedures. Patients with the Blalock-Taussig shunt (subclavian to pulmonary artery) have a much lower risk of pulmonary vascular disease.[3] The modified Blalock-Taussig shunt uses a Gore-Tex conduit to maintain perfusion to the arm.

The Rastelli procedure involves an extracardiac conduit from the right ventricle to the pulmonary artery to improve pulmonary artery blood flow in patients with atretic pulmonary valves. Formerly these conduits contained a heterograft or mechanical prosthetic valve; the current use of homograft valve conduits will hopefully avoid the problems caused by valvular obstruction or degeneration.[27]

In summary, the palliative procedures employed in these patients are associated with substantial morbidity and mortality, necessitating continued clinical and noninvasive surveillance.

Medical Considerations in Congenital Heart Disease

Eisenmenger's Syndrome

The development of pulmonary hypertension in the presence of increased pulmonary blood flow due to an intracardiac communication results in Eisenmenger's "syndrome" in which the shunt flow reverses (right to left), causing cyanosis. The primary conditions leading to this syndrome include ventricular septal defect, ostium primum atrial septal defect, atrioventricular canal defect (otherwise known as the endocardial cushion defect), aortopulmonary window, and patent ductus arteriosus. Eisenmenger's syndrome usually develops before puberty, but occasionally patients with ostium secundum defects acquire pulmonary vascular disease after puberty.[6]

Complications include the development of secondary polycythemia, an associated bleeding diathesis, hyperuricemia, and gout.[28] Phlebotomy is generally not recommended if there are no symptoms and if the hematocrit is below 0.65 (65%). The use of heparin and aspirin should be avoided because of the bleeding diathesis. Gout can be treated with conventional therapy, with care to avoid the antiplatelet properties of anti-inflammatory agents.[28] Pregnancy is accompanied by an unacceptably high rate of maternal and fetal mortality and is virtually contraindicated in patients with Eisenmenger's syndrome.

Surgical repair of the primary defect is contraindicated in the presence of severe pulmonary vascular disease; however, improved results in heart-lung transplantation offer an alternative for adolescents and young adults with Eisenmenger's syndrome. In addition, early results in children with lung transplantation and intracardiac repair are promising.[29]

Other Considerations

With many men and women with congenital heart disease entering their reproductive years, genetic counseling and other issues regarding pregnancy are important. The risk of congenital heart defects is increased to about 10% in their offspring (higher in specific disorders).[30,31] Therefore, fetal echocardiography is mandated when either parent or siblings are affected.[32] Maternal and fetal mortality vary with functional class and are highest in Eisenmenger's syndrome.[32]

Recommendations regarding exercise can generally follow those outlined in the 26th Bethesda Conference but should be tailored to the individual patient following a complete clinical and noninvasive evaluation.[33] Substantial asymptomatic arrhythmias should be excluded by exercise testing and Holter monitoring.

Acquired heart disease may interact with congenital heart disease in unexpected ways, and it is important not to ignore its presence. For example, it is well known that the progression of atherosclerotic coronary disease may be accelerated when aortic coarctation is present. Thus, physicians are obligated to attend to the management of coronary risk factors and to treat hypertension in adults with congenital heart disease.

Summary

The increased number of patients and the diversity of congenital heart defects present a challenge for general internists, family physicians, and cardiologists. The long-term sequelae in both operated and unoperated cases necessitate ongoing surveillance. Additional issues faced by patients and physicians include pregnancy, exercise tolerance, insurability, and the psychosocial manifestations of a chronic illness.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 429)

February 19-22—**Clinical Hematology and Oncology: 1996.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Department of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders**. Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii, on Mon-Fri. 26 hrs. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

January 27—**Genetic Disease & the Eye.** Cedars-Sinai Medical Center at Hotel Sofitel, Los Angeles. Sat. 7 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Room 2211, Los Angeles 90048. (310) 855-2937.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists.** Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Saturday. 7 hrs. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037 (619) 554-8556.

OTOLARYNGOLOGY

February 3-7, March 2-6, April 13-17—**Temporal Bone Dissection Course.** House Ear Institute in Los Angeles. 48 hrs. $1300. Contact: Antonio De la Cruz, 2100 W. Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists**. Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, P O Box 1216, Murrieta, CA 92564. (909) 677-4482.

PATHOLOGY

March 18-20—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Mon-Wed. 20 hrs. $500. Contact: UCSD

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 554-8556.

PEDIATRICS

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

January 19-21—**Practical Pediatric Electrophysiology and Pacing Course.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. Contact: Children's Hospital and Health Center, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 22-26—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital and Health Center at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. Contact: Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 26-28—**34th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. $295. Contact: David Steward, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 19-21— **Pediatric Update**. Continuing Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego, 92138. (619) 223-2997.

March 1-3—**Current Concepts in Pediatric Medicine**. Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

March 28-30—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 11 hrs. $350. Contact: UCSD.

PLASTIC SURGERY

December 8-9—**2nd Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources. Fri-Sat. Contact: Martin Borsanyi, c/o Professional Image, (714) 760-1522.

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face**. UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

January 21-26—**22nd Annual Midwinter Program in Continuing Medical Education for Psychiatrists**. UC Davis at Hyatt Regency, Incline Village, NV. Sun-Fri. 25 hrs. $425-$495. Contact: UC Davis.

February 11-13—**29th Annual Recent Advances in Neurology**. UCSF at Ritz-Carlton, San Francisco. Sun-Tues. Contact: UCSF

February 12-17—**AGPA National Conference and Institute: Toward Total Health: Groups to Heal the Mind and Body.** Northern California Group Psychotherapy Society at San Francisco. Mon-Sat. Contact: Ann Steiner, Ph.D., NCPGS, 821 East Second St., Ste. 203, Benicia 94510. (415) 442-1976.

April 19-21—**West Coast Neuropsychology Conference**. UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. 15.5 hrs. $325. Contact: UCSD.

PULMONARY/CRITICAL CARE

December 1-2—**Laser Bronchoscopy, Stents, Brachytherapy, Thoracoscopy for the Pulmonologist and Emphysema Surgery.** MMC/UCI Center for Health Education at Long Beach Memorial Medical Center. Fri-Sat. Contact: Center for Health Education, (310) 933-3811.

RADIOLOGY

November 2-4—**8th Annual Obstetrical and Transvaginal Ultrasound Course—A Hands-On Course**. MMC/UCI Center for Health Education at Doubletree Hotel, Orange. Thurs-Sat. Contact: Center for Health Education, (310) 933-3811.

January 28-29—**Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel Del Coronado San Diego. Sun-Mon. 16 hrs. $375. Contact: UCSD.

January 28-February 4—**Multispecialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest Ultrasound, and Bone.** UCSD at Hotel del Coronado, San Diego. 1 wk. 40 hrs. Contact: UCSD.

March 10-15—**Neuro- and Musculoskeletal MR**. UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $425-$625. Contact: UCSD.

March 10-15—**Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $626. Contact: UCSD.

March 10-15—**General Radiology Review Course.** UCLA at Guest Quarters Suite Hotel in Santa Monica. Sun-Fri. 40 hrs. $420. Contact: UCLA.

April 6—**Spring Invasive Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. Contact: UCSD.

April 7-12—**16th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $700. Contact: UCSD.

April 7- 12—**UCSD Neuro & Musculoskeletal MR Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

April 12-14—**2nd Annual Breast Imaging & Interventions Course**. UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

SURGERY

December 1-3—**International Symposium on TMJ Arthroscopy and Arthroscopic Surgery**. Fri-Sun. $695. Contact: Peg Hoelderlin, c/o Professional Image, (714) 760-1522.

January 5-9—**19th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Pan Pacific Hotel, San Diego. Tues-Fri. 26 hrs. $475. Contact: UCSD.

January 12-13—**What's New In General Surgery: 18th Annual Postgraduate Course.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $285. Contact: UCD.

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February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in LA Jolla. Sat. 7 hrs. $140. Contact: Dept. of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037-(619) 554-8556.

February 19-22—**Clinical Hematology and Oncology: 1966**. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Department f Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, 92037. (619) 554-8556.

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

December 23-29—**Advances in Medicine 1995**. Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Fri. 6 hrs. $475. Contact: Symposium Maui, PO Box 10185, Lahaina, HI 96761. (808) 661-8032.

January 17-20—**Medicine Meets Virtual Reality 4: Health Care in the Information Age—Future Tools for Transforming Medicine**. UCSD at San Diego Convention Center. Wed-Sat. 23 hrs. $450. Contact: UCSD.

February 19-23—**Physician Heal Thyself**. UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

March 2—**The Neuropharmacology of Sleep Medicine.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037. (619) 554-8556.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 1-3—**Your Passport to the Future in Internal Medicine.** American College of Physicians/Colorado Chapter at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deb Foust, ACP, Colorado Chapter, (303) 837-7837.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 1-2—**Trauma Update 1995.** Hilton Hotel Albuquerque, Contact: Carol Glavey, UNM SOM.

December 7-9—**American College of Physicians, New Mexico Chapter, and New Mexico Society of Internal Medicine—Scientific Session**. Hilton Inn, Albuquerque. Contact: Carol Case, UNM SOM.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Fri-Sat. Contact: Billie Dytzel, (505) 265-0732.

February 24-25—**Mammography: Practical Challenges of the 90s for the Technologist.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Sat-Sun. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax (404) 552-9859.

February 24-25—**Mammography: Practical Challenges of the 90s for the Technologist.** The La Fonda Hotel Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax, (404) 552-9859.

February 24-27—**Mammography: Practical Challenges of the '90s: Managed Care, MQSA, and the Radiologist's New Role as Care Giver.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. Fax, (404) 552-9859.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe. Santa Fe. Contact: UNM SOM

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth

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South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 3-6—**Arthritic Hip, Knee, and Shoulder Symposium.** UUSM Dept of Orthopedics at Snowbird Resort, Snowbird. Contact: UnConventional, Inc, (619) 279-9955 or fax (619) 279-1130.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Contact: UUMS.

March 4-8—**Advances in Internal Medicine.** Snowbird. Contact: UUSM.

March 10-15—**18th Annual Winter Psychiatry Conference: New Perspectives in Clinical Practice**. The Menninger Clinic at The Yarrow, Park City. Sun-Fri. 28 hrs. $345. Contact: (800) 288-7377.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 1—**Pediatrics Update**. Seattle. Fri. Contact: VMMC.

December 1—**Infectious Disease Update.** Tacoma. Fri. Contact: PCMS CME.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 2—**Fiberoptic Intubation.** Seattle. Sat. Contact: U/W.

December 7-8—**ACLS.** Tacoma. Thur-Fri. Contact: PCMS CME.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9—**Fiberoptic Intubation**. Seattle. Sat. Contact: U/W.

December 14—**Clinical Recognition of Health Hazards in the Home.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety.

December 14-16—**Primary Care for the Ob/Gyn**. Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference**. Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

January 11-12—**Ergonomics.** Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 20—**Pharmacology Update.** Seattle. Sat. Contact: Swedish Hospital, (206) 386-2265.

January 25—**Ethical Issues in Occupational Health**. Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 31-February 4—**CME at Whistler, Canada**. Wed-Mon. Contact: PCMS CME.

February 5-9—**Hazardous Waste Annual Refreshers**. Seattle. Mon-Fri. Contact: NW Center for Occupational Health & Safety, (206) 543-1069.

February 22—**Risk Assessment**. Seattle. Thur. Contact: NW Center for Occupational Health & Safety, (206) 543-1069.

February 23—**Risk Communication.** Seattle. Fri. Contact: NW Center for Occupational Health & Safety, (206) 543-1069.

February 23—**Review of HIV Infections**. Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

THE WESTERN JOURNAL OF MEDICINE

ISSN #0093-0415 PUBLISHED SINCE 1904 TAX ID 94-0359340

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Applications are due January 12, 1996, for funds starting June 1, 1996. For copies of the Cycle II call for applications and the complete Application Packet, contact the BCRP office by letter, phone, fax, e-mail or the Internet; or attend one of the information meetings scheduled in early November at various locations around the state.

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Arizona Medical Association, Inc–810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1996, Scottsdale Plaza Resort, Scottsdale.

California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 1-5, 1996, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 20-22, 1996, Steam Boat Sheraton, Steam Boat Springs.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1996, Sun Valley Inn, Sun Valley, Idaho.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, New Mexico Medical Society Offices, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 25-28, 1996. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 26-28, 1996. Tacoma Sheraton, Tacoma.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1996, Jackson Lake Lodge, Moran.

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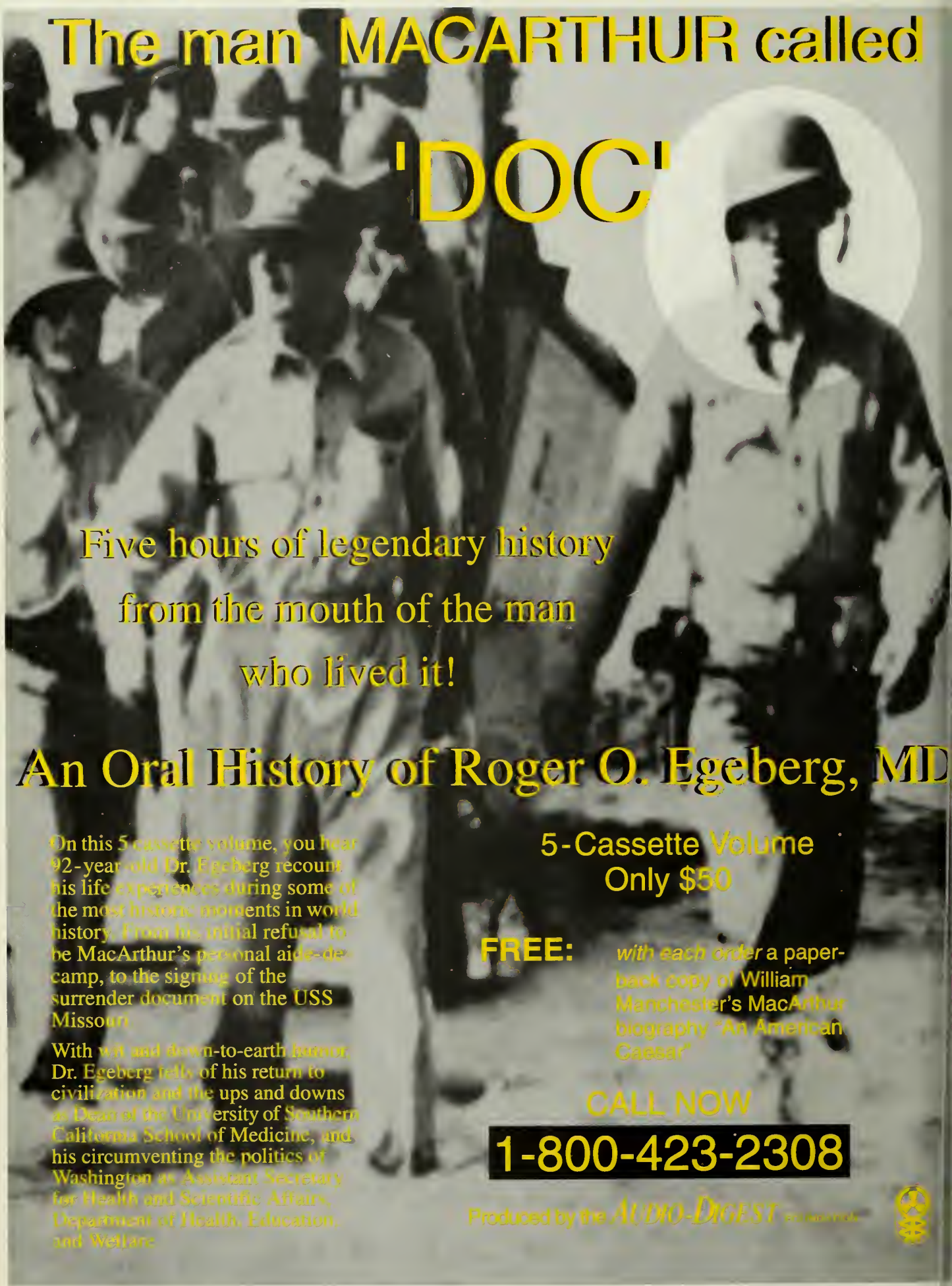

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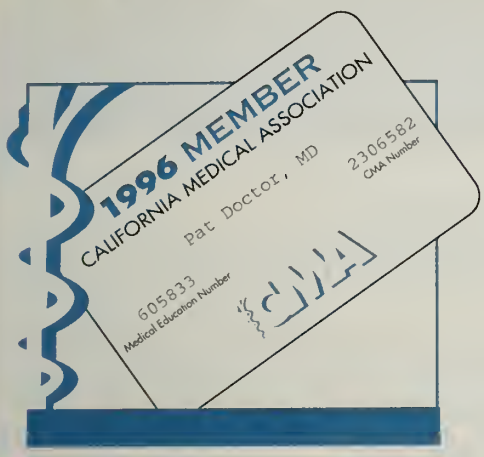

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"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style appears in most issues. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

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SPRING 1996 CALENDAR

February 16-18	**2nd Annual New Drugs Update: Indications, Interactions, Efficacy and Cost Analysis** Hotel Nikko, Atlanta, GA
March 7-10	**Sixth Annual SEC Sports Medicine Symposium** Fairmont Hotel, New Orleans, LA
March 29-31	**Update on Emergency Medicine & Acute Burn Care** Amelia Island Plantation, Amelia Island, FL
April 26-28	**Common Clinical and Practice Skills: Use and Interpretation** Ritz-Carlton – Buckhead, Atlanta, GA
May 3-5	**Emerging Trends in Infectious Diseases: A Problem-Based Symposium** Sheraton Charleston Hotel, Charleston, SC
May 16-18	**Sixth Annual Current Concepts in Orthopaedics** Omni Inner Harbor Hotel, Baltimore, MD

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The Western Journal of Medicine

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The Western Journal of Medicine

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 11-14—**6th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Thurs-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 13—**High-Dose Chemotherapy & Bone Marrow Transplantation in the Management of Breast & Ovarian Cancer.** University of Arizona College of Medicine at the Red Lion's La Posada Resort, Scottsdale. Sat. Contact: U of A.

January 16-20—**Phoenix Surgical Society—24th Annual Meeting**. Phoenician Resort, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

January 19-21—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 19-21—**The Scottsdale Headache Symposium: Headache and Face Pain.** American Association for the Study of Headache at the Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: (609) 845-1720.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 11-15—**International Congress IX on Endovascular Interventions**. Arizona Heart Institute and International Society for Endovascular Surgery at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: Erika Scott, (602) 266-2200.

February 12-16—**5th Annual Psychopharmacology Review**. University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

February 15-17—**Mayo Interactive Surgical Symposium**. Mayo Foundation at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Trish Ghan, (602) 301-8323.

February 16-18—**Arizona Society of Anesthesiologists: Anesthesia for the '90s.** University of Arizona College of Medicine at the Doubletree Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: U of A.

February 17—**Ninth Epilepsy Update: Seizures at All Ages.** University of Arizona College of Medicine at the Austin La Paloma Resort, Tucson. Sat. Contact: U of A.

February 19-22—**State-of-the-Art Echocardiography (1626).** American College of Cardiology at Sheraton El Conquistador, Tucson. Mon-Thurs. 25.5 hrs. Contact: (800) 257-4739.

February 22-24—**5th Biennial Geriatric Medicine Update and Certification Exam Review Course.** University of Arizona College of Medicine at The Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

March 3-6—**10th Annual Magnetic Resonance Imaging Conference.** St Joseph's Hospital and Medical Center and Barrow Neurological Center at the Phoenician Resort, Scottsdale. Sun-Wed. Contact: (602) 406-3067.

March 7-9—**23rd Annual Symposium: Recent Advances in Neurology & Neurosurgery.** St Joseph's Hospital and Medical Center and Barrow Neurological Institute at the Phoenician Resort, Scottsdale. Thurs-Sat. Contact: (602) 406-3067.

March 7-10—**19th Annual Mid-Winter Symposium: Advances in Obstetrics & Gynecology**. Maricopa Medical Center and Phoenix OB/GYN at the Radisson Resort Hotel, Scottsdale. Thurs-Sun. Contact: Cathy Clifton, (602) 267-5366.

March 10-14—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at the Marriott's Camelback Inn, Scottsdale. Sun-Thurs. Contact: Vivian Woods, (313) 763-1400.

March 13-16—**International Conference on the Adjuvant Therapy of Cancer.** University of Arizona College of Medicine at the Wyndham Paradise Valley Resort, Scottsdale. Wed-Sat. Contact: U of A.

March 21-23—**Ophthalmic Reviews 1996: Oculoplastics From Coast to Coast.** Mayo Clinic-Scottsdale at the Radisson Resort, Scottsdale. Thurs-Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

March 28-30—**5th Annual Urogynecology and Disorders of the Female Pelvic Floor.** Mayo Clinic-Scottsdale at The Points Hilton Resort at Tapatio Cliffs, Phoenix. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

April 9-13—**New Frontiers in Pain.** Maricopa Medical Center at the Radisson Resort Hotel, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

April 10-13—**21st Annual Primary Care Update.** University of Arizona College of Medicine at the Tucson Hilton East, Tucson. Wed-Sat. Contact: U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724, (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 30-February 3—**34th Annual Scientific Session of the Western Society of Allergy and Immunology**. Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, PO Box 1122, Roanoke, TX 76262. (817) 491-2616.

ANESTHESIOLOGY

January 10-13—**UCSD Anesthesia Update**. UCSD at Hotel del Coronado. Wed-Sat. 21 hrs. $375. Contact: UCSD.

January 11-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. 2 wks. 20 hrs. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City, CA 94404. (800) 345-3691.

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(Continued from Page 518)

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 26-29—**5th John J. Bonica Hawaii Pain Conference**. Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

January 26-28—**Clinical Nuclear Cardiology: Case Review With the Experts**. Cedars-Sinai Medical Center at Los Angeles. Fri-Sun. 17.5 hrs. Contact: (800) 257-4739.

February 9-10—**Cardiology 1996: Concepts and Controversies.** Mercy General Hospital at Radisson Hotel, Sacramento. Fri-Sat. 7 hrs. Contact: Andrea La Pravotte, Mercy Heart Institute. (916) 733-6966.

February 12-16—**Cardiovascular Conference at Hawaii.** American College of Cardiology at Kohala Coast, Hawaii. Mon-Fri. 20.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739. FAX (301) 897-9745.

March 2-9—**Update: Controversies in Cardiovascular Disease.** UCSD at Stouffer Wailea Resort, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

April 25-27—**Sixth Annual Symposium on Coronary Stenting.** Scripps Clinic & Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 15-19—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 17—**California Trauma Conference, Trauma Coordinator Symposium.** UCD at Hyatt Regency Hotel, Sacramento. Wed. 6 hrs. $20. Contact: UCD.

January 18-20—**California Trauma Conference**. UCD at Hyatt Regency, Sacramento. Thurs-Sat. 17 hrs. $425. Contact: UCD.

February 12-16—**34th Annual Symposium on Critical Care, Trauma, and Emergency Medicine.** USC at the Las Vegas Hilton Hotel. Mon-Fri. 26.75 hours. $595. Contact: USC.

February 24-March 2—**Pediatric Emergencies**. UCSD at Royal Lahaina, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

March 18-22—**Emergency Medicine Symposium II**. UCSD and BSB at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 27-29—**12th Annual Advances in Emergency Medicine.** USC at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17 hrs. $495. Contact: USC.

May 31-June 6—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. 18 hrs. $250. Contact: USC.

ENDOCRINOLOGY/METABOLISM

March 13-14—**Advances in Endocrinology and Metabolism.** UCSF at Ana Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $320. Contact: UCSF.

March 15-16—**Diabetes Update.** USC at Ana Hotel, San Francisco. Fri-Sat. 10.5 hrs. $255. Contact: USC.

June 7-11—**Molecular Steriodogenesis**. UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Diseases.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. Contact: UCSF.

January 25-27—**Third Annual Epidemiology and Prevention of Infectious Diseases.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 14.5 hrs. $445. Contact: UCSF.

May 1-3—**17th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17.5 hrs. $410. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

January 19-21—**Dermatology for the Non-Dermatologist**. Continuing Medical Education Associates at Hyatt Regency La Jolla, San Diego. Fri-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

January 20-27—**Sports Medicine.** UCSD at Royal Waikoloan, Kona, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

January 22-24—**Ophthalmology and ENT for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Primary Care Dermatology**. UCSD at Hilton Beach and Tennis Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: UCSD.

February 1-3—**Neurology for the Non-Neurologist.** UCSD. Thurs-Sat. 21 hrs. $500. Contact: UCSD.

February 16-18—**Office Gynecology and Women's Health for the Primary Care Physician**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

February 17-23—**Perinatal Medicine.** USC at Westin Maui, Hawaii. Mon-Thurs. 20 hrs. $595. Contact: USC.

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

March 20-22—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 15 hrs. $325. Contact: UCSF.

April 1-4—**Primary Care in Paradise: Maui 1996.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 6-13—**Sixth Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kauai Marriot Resort, Kauai, Hawaii. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez, CA 94553. (510) 372-1457.

April 7-12—**Ninth Annual Primary Care Medicine: Update 1996**. UCSF at Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

April 18-21—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hilton Beach and Tennis Resort, San Diego. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 27—**29th Society of Teachers of Family Medicine Annual Spring Conference.** AAFP and Society of Teachers of Family Medicine at The Hyatt Regency at Embarcadero Center, San Francisco. Sat-Wed. Contact: Ray Rosetta, Director of Meetings and Programs, The Society of Teachers of Family Medicine. (800) 274-4512.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

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May 17-21—**Essentials in Primary Care**. Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

March 2-3—**Gastroenterology 1996**. The Southern California Society for Gastrointestinal Endoscopy and the Southern California Gastroenterology Society Symposium. SCGSS at Century Park Hotel, San Francisco. Sat-Sun. Contact: Joyce M. Fried, 19327 Pauma Valley Dr, Northridge, CA 91326. FAX (310) 312-9279.

GERIATRICS

January 18-20—**Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton, Beverly Hills. Thurs-Sat. 30 hrs. $525. Contact: UCLA.

INTERNAL MEDICINE

February 9-10—**Advances in Diagnosis and Treatment of Splenic Disorders.** Cedars-Sinai Medical Center at Hotel Sofitel Los Angeles. Fri-Sat. 11.5 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937.

February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in La Jolla. Sat. 7 hrs. $140. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 14-16—**29th Annual Recent Advances in Neurology**. UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $375. Contact: UCSF.

February 17-22—**Topics and Advances in Internal Medicine**. UCSD at San Diego Marriott. Sun-Thurs. 50 hrs. $595. Contact: UCSD.

March 9-16—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kameula, Hawaii. Mon-Fri. 28 hrs. $595. Contact: USC.

March 15-21—**Internal Medicine 1996.** Continuing Medical Education Associates at the Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 11-13—**Recent Advances in Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. Contact: UCSD.

April 20—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 6 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

May 9-10—**Practical Aspeets of Caring for Alzheimer's Disease Victims.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

MANAGED CARE

January 19-21—**Neurosurgery, Government, and Managed Care: Adapting to a Changing Environment.** California Association of Neurological Surgeons at Hyatt Regency Hotel, Sacramento. Fri-Sun. Contact: Janine Tash, California Association of Neurological Surgeons. (916) 443-0236.

January 26-27—**Advanees in Pulmonary Medicine: Medical Care to Managed Care.** California Thoracic Society at Le Meridien San Diego at Coronado. Fri-Sat. 10 hrs. Contact: California Thoracic Society, 202 Fashion Ln #219, Tustin 92680. (714) 730-1944.

NEPHROLOGY

January 31-February 3—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Regency on the Bay, San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

February 10-13—**51st Annual Postgraduate OB/GYN Assemhly**. Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Sat-Tues. 22 hrs. Contact: Director, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

January 29-February 2—**Occupational & Environmental Medicine I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

ONCOLOGY

February 19-22—**Clinical Hematology and Oncology: 1996.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders**. Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii, on Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

January 27—**Genetic Disease & the Eye.** Cedars-Sinai Medical Center at Hotel Sofitel, Los Angeles. Sat. 7 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd. Room 2211, Los Angeles 90048. (310) 855-2937.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists.** Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

OTOLARYNGOLOGY

February 3-7, March 2-6, April 13-17—**Temporal Bone Dissection Course.** House Ear Institute in Los Angeles. 48 hrs. $1,300. Contact: Antonio De la Cruz, MD, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext 7079.

February 23-25—**65th Midwinter Clinical Conferenee for Ophthalmologists and Otolaryngologists**. Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

June 22-28—**1995-1996 Skull Base Surgical Dissection Course**. House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles, CA 90057.

June 29-July 4—**Seeond International Skull Base Congress and the Seventh Annual Meeting of the North Ameriean Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Fl, Los Angeles 90057.

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PATHOLOGY

March 18-20—**Current Issues in Blood Substitute Research and Development.** UCSD at Sheraton Harbor Island, San Diego. Mon-Wed. 20 hrs. $500. Contact: UCSD

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 23-25—**Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

January 19-21—**Practical Pediatric Electrophysiology and Pacing Course.** Children's Hospital and Health Center at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.75 hrs. Contact: Children's Hospital and Health Center, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 22-26—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital and Health Center at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs. Contact: Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (619) 495-4940.

January 26-28—**34th Clinical Conference in Pediatric Anesthesiology**. Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. $295. Contact: David Steward, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

February 19-21— **Pediatric Update**. Continuing Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 1-3—**Current Concepts in Pediatric Medicine**. Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

March 28-30—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 11 hrs. $350. Contact: UCSD.

April 21-23—**Weaning '96.** USC at Stouffer Renaissance Esmeralda Resort, Palm Springs. Sun-Tues. 10 hrs. $525. Contact: USC.

May 16-18—**29th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 16 hrs. $350. Contact: UCSF.

PLASTIC SURGERY

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face**. UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

January 21-26—**22nd Annual Midwinter Program in Continuing Medical Education for Psychiatrists**. UC Davis at Hyatt Regency, Incline Village, NV. Sun-Fri. 25 hrs. $425-$495. Contact: UC Davis.

February 11-13—**29th Annual Recent Advances in Neurology**. UCSF at Ritz-Carlton, San Francisco. Sun-Tues. Contact: UCSF.

February 12-17—**AGPA National Conference and Institute: Toward Total Health: Groups to Heal the Mind and Body.** Northern California Group Psychotherapy Society at San Francisco. Mon-Sat. Contact: Ann Steiner, PhD, NCPGS, 821 E Second St, Ste 203, Benicia 94510. (415) 442-1976.

February 23-24—**Psychopharmocology: When to Use What.** American Psychiatric Association and Nevada Association of Psychiatric Physicians at Golden Nugget Hotel, Las Vegas. Fri-Sat. 16 hrs. Contact: Robert L. Horne, MD, 6000 W Rochelle, Ste 700, Las Vegas 89103. (702) 364-1177. FAX (702) 364-5060.

April 19-21—**West Coast Neuropsychology Conference**. UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. 15.5 hrs. $325. Contact: UCSD.

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS, (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla CA 92037. (619) 554-8556.

RADIOLOGY

January 28-29—**Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sun-Mon. 16 hrs. $375. Contact: UCSD.

January 28-February 4—**Multispecialty Radiology Courses: Neuroradiology, Angiographic, Interventional, Chest Ultrasound, and Bone.** UCSD at Hotel del Coronado, San Diego. 1 wk. 40 hrs. Contact: UCSD.

March 10-15—**Neuro and Musculoskeletal MR**. UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $425-$625. Contact: UCSD.

March 10-15—**Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $626. Contact: UCSD.

March 10-15—**General Radiology Review Course.** UCLA at Guest Quarters Suite Hotel in Santa Monica. Sun-Fri. 40 hrs. $420. Contact: UCLA.

April 6—**Spring Invasive Radiology**. UCSD at Hotel del Coronado, San Diego. Sat. Contact: UCSD.

April 7-12—**16th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $700. Contact: UCSD.

April 7- 12—**UCSD Neuro & Musculoskeletal MR Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

April 12-14—**2nd Annual Breast Imaging & Interventions Course**. UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

SURGERY

January 5-9—**19th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Pan Pacific Hotel, San Diego. Tues-Fri. 26 hrs. $475. Contact: UCSD.

January 12-13—**What's New In General Surgery: 18th Annual Postgraduate Course.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 14 hrs. $285. Contact: UCD.

February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in La Jolla. Sat. 7 hrs. $140. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 19-22—**Clinical Hematology and Oncology: 1996**. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 28-March 3—A **Divisional Affiliate of the American Osteopathic Association at Palm Springs Riviera Resort**. Wed-Sun. 37 hrs. $495-$745. Contact: Linda Wahlen, Meeting Planner, Osteopathic Physicians and Surgeons of California, 455 Capital Mall, Ste 230, Sacramento, 95804. (916) 447-2004. FAX (916) 447-4828.

March 21-23—**Eighth Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $350-$950. Contact: UCSF.

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

January 17-20—**Medicine Meets Virtual Reality 4: Health Care in the Information Age—Future Tools for Transforming Medicine**. UCSD at San Diego Convention Center. Wed-Sat. 23 hrs. $450. Contact: UCSD.

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February 19-23—**Physician Heal Thyself.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

March 2—**The Neuropharmacology of Sleep Medicine.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037. (619) 554-8556.

May 31-June 2—**38th Annual Scientific Meeting of the American Association for the Study of Headache.** San Diego. Fri-Sun. Contact: AASH, (619) 845-1720.

August 8-11—**38th Annual Postgraduate Refresher Course-Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams St, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 25-27—**Medical Disorders During Pregnancy.** University of Colorado Health Sciences Center at Beaver Run Resort, Breckenridge. Thur-Sat. Contact: U of Colo.

February 1-3—**Your Passport to the Future in Internal Medicine.** American College of Physicians/Colorado Chapter at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deb Foust, ACP, Colorado Chapter, (303) 837-7837.

February 18-23—**22nd Annual Vail Obstetrics and Gynecology Conference.** University of Colorado Health Sciences Center at Vail. Sun-Fri. Contact: U of Colo.

March 1-8—**Colorado Review of Anesthesia.** University of Colorado Health Sciences Center at Marriott's Vail Mountain Resort. Fri-Fri. Contact: U of Colo.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

March 10-13—**International Conference on the Fetus and Newborn XXX: Novel Therapies for Neonatal Respiratory Disorders.** University of Colorado Health Sciences Center at Aspen. Sun-Wed. Contact: U of Colo.

March 17-22—**Reconstructive Surgery of the Hip and Knee.** University of Colorado Health Sciences Center at the Ritz-Carlton Hotel. Aspen. Sun-Fri. Contact: U of Colo.

March 23-28—**Geriatrics Board Review Course.** University of Colorado Health Sciences Center at Denver. Sat-Thurs. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

February 16-18—**37th Annual Medical Winter Clinics.** Ada County Medical Society at Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. Contact: Judy Barningham, (208) 336-2930 or Marie Chester, (208) 386-2135.

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Ste 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting.** Santa Fe. Fri-Sat. Contact: Billie Dytzel, (505) 265-0732.

February 24-25—**Mammography: Practical Challenges of the '90s for the Technologist.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Sat-Sun. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. FAX (404) 552-9859.

February 24-28—**Mammography: Practical Challenges of the '90s: Managed Care, MQSA, and the Radiologist's New Role as Care Giver.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Sat-Wed. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. FAX (404) 552-9859.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe. Santa Fe. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the

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American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 3-6—**Arthritic Hip, Knee, and Shoulder Symposium.** UUSM Dept of Orthopedics at Snowbird Resort, Snowbird. Contact: UnConventional, Inc, (619) 279-9955 FAX (619) 279-1130.

February 7-10—**Cardiovascular Conference at Snowbird.** Wed-Sat. 19 hrs. Contact: (800) 257-4739.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Contact: UUMS.

February 24-28—**37th Annual OB/GYN Update.** Park City. Contact: UUSM.

February 28-March 2—**Maternal-Fetal Medicine Update.** Park City. Contact: UUSM.

March 4-8—**Advances in Internal Medicine.** Snowbird. Contact: UUSM.

March 10-15—**18th Annual Winter Psychiatry Conference: New Perspectives in Clinical Practice**. The Menninger Clinic at The Yarrow, Park City. Sun-Fri. 28 hrs. $345. Contact: (800) 288-7377.

MEDICAL GRAND ROUNDS

January 3-7—**Advances in Endoscopy and Minimally Invasive Surgery.** Park City. 24 hrs. Contact: UUSM.

January 26-27—**Management of the Dizzy Patient.** University Park Hotel, Salt Lake City. 6 hrs. Contact: UUSM.

February 3-6—**Physical Medicine and Rehabilitation Update.** Olympia Park Hotel, Park City. 16 hrs. Contact: UUSM.

February 3-7—**Clinical Cardiac Electrophysiology Review.** Cliff Lodge at Snowbird, Salt Lake City. 35 hrs. Contact: UUSM.

February 5-9—**Surgical Pathology.** Yarrow Hotel at Park City. 20 hrs. Contact: UUSM.

March 28-30—**4th International Congress on Alport Syndrome.** University Park Hotel, Salt Lake City. Contact: UUSM.

April—**Advanced Techniques in Laryngeal Surgery.** 40 hrs. Contact: UUSM.

April 27—**Advances in the Management of Pain in the Acute and Chronic Settings.** University Park Hotel, Salt Lake City. 6 hrs. Contact: UUSM.

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 11-12—**Ergonomics**. Seattle. Thurs-Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

January 20—**Pharmacology Update**. Seattle. Sat. Contact: Swedish Hospital, (206) 386-2265.

January 25—**Ethical Issues in Occupational Health**. Seattle. Mon-Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

January 31-February 4—**CME at Whistler, Canada**. Wed-Mon. Contact: PCMS CME.

February 5-9—**Hazardous Waste Annual Refreshers**. Seattle. Mon-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 22—**Risk Assessment**. Seattle. Thur. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 23—**Risk Communication.** Seattle. Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 23—**Review of HIV Infections**. Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Division of Continuing Medical Education, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. ◆

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Articles

Physician-Patient Communication in Managed Care

GEOFFREY H. GORDON, MD; LAURENCE BAKER, PhD; *and* WENDY LEVINSON, MD, *Portland, Oregon*

The quality of physician-patient communication affects important health care outcomes. Managed care presents a number of challenges to physician-patient communication, including shorter visits, decreased continuity, and lower levels of trust. Good communication skills can help physicians create and maintain healthy relationships with patients in the face of these challenges. We describe 5 communication dilemmas that are common in managed care and review possible solutions suggested by recent literature on physician-patient communication. We also describe ways that managed care plans can promote more effective communication between physicians and patients.

(Gordon GH, Baker L, Levinson W: Physician-patient communication in managed care. West J Med 1995; 163:527-531)

The physician-patient relationship, characterized by mutual respect and understanding, is the cornerstone of medical care.[1] Good physician-patient communication, using skills that best express these characteristics, improves biologic and psychosocial health care outcomes and enhances patient satisfaction.[2-4] A breakdown in communication is frequently cited by patients as a reason to change physicians, disenroll from health care plans, or initiate malpractice litigation.[5-8]

Managed care presents a number of new challenges to physician-patient communication.[9-11] First, long-standing relationships may be restricted or nullified as patient and physician groups "change hands" in the managed care market. Second, productivity requirements may reduce the amount of time physicians spend with patients, eliminating or curtailing effective communication. Third, patients may join managed care plans with unrealistic expectations and a sense of entitlement. If patients expect their "money's worth" while the plan encourages physicians to limit costs and use, both parties may lose trust in each other, feel "trapped" by the plan, and seek administrative rather than clinical solutions to problems. Finally, some managed care physicians are less satisfied than those in fee-for-service settings, in part because of frustrations with physician-patient communication.[12-14]

The following are brief statements made by patients to their physicians. Each statement portrays a common dilemma in communication between physicians and patients that is especially problematic in managed care. Following each statement is a brief description of techniques and procedures suggested by recent literature on physician-patient communication. The goal of these techniques and procedures is to preserve the essential features of the physician-patient relationship in the face of challenging managed care environments.

Too Many Problems, Too Little Time

"Oh, by the way, Doctor, I still have a few other things bothering me. You're not going to rush out the door again, are you? Can't we talk for more than 10 minutes?"

This patient expects to talk with the physician for more than ten minutes, the usual time allotted for a return visit in many managed care settings. The physician's goal in this situation is to help the patient feel "heard" without sacrificing efficiency. Sitting down, making eye contact, and removing physical barriers to communication simply but powerfully facilitate rapport.[15] Allowing patients to finish their opening statements without interruption rarely takes more than several minutes and establishes the importance of their concerns and subsequent participation in care.[16,17] Many patients tell brief stories about their illnesses; allowing them to proceed without interruption helps them to feel understood and respected, an important first step in care.[18,19]

Because some patients save the most serious or difficult problems for last, inviting patients to "put all their cards on the table" early in the visit can improve patient satisfaction and reduce the chance of new symptoms being introduced at closure.[20,21] Once all of a patient's concerns and requests are aired, a realistic agenda for the visit can usually be consensually negotiated. One way to help patients prioritize is to ask them which concerns are most important to address before they leave the office that day.

For patients with emotionally distressing problems, physicians' empathic skills can be therapeutic without sacrificing efficiency. Five elements of empathic communication have been described[22]:

- Reflection: "You're really feeling overwhelmed by all these symptoms";

From the Medical Service, Portland Veterans Affairs (VA) Medical Center (Drs Gordon and Baker), and the Legacy Good Samaritan Hospital (Dr Levinson), the Oregon Health Sciences University School of Medicine, and the Northwest Center for Physician-Patient Communication, Portland.

Reprint requests to Geoffrey H. Gordon, MD, VA Medical Center, Medical Service (111P), 3710 SW US Veterans Hospital Rd, Portland, OR 97201.

- Legitimation: "I can imagine how upsetting it must be";
- Respect: "You've been doing your best to cope";
- Support: "I'd like to help"; and
- Partnership: "Maybe we can work on these one at a time."

Contrary to some physicians' fears, patients' expressions of emotion are often brief, self-limited, and responsive to direction by their physician.[23] Physicians' use of empathic skills does not prolong the visit substantially and is associated with greater patient satisfaction.[24,25]

Finally, some patients who expect more time need an initial orientation and subsequent redirection to the process of the visit. The following illustrates this approach: "When our time together is limited, it's even more important that we work as a team. Right now we need to decide early on what to work on today and what can wait. I'll make sure you have time to tell me your concerns and also to hear what I think we should do."

Interruptions, repetitions, and stereotyping—"So you're *that* kind of doctor [or patient] . . ."—by either party are early warning signs of communication breakdown. If they occur, consider acknowledging that a problem exists and inviting the patient's input: "I think we both want to understand each other, but we're having trouble doing it. How can we get back on track?"

Misguided Requests

"I always need antibiotics to get over these colds. I can't miss any more time at work, and the wife says, 'Don't come home without the pills.' That's why we signed up for this health plan."

This patient has specific ideas about what is wrong and what needs to be done about it. His wife acts as an informal health advisor. Finally, he feels entitled to request services as a subscriber to his health plan.

Most patients have beliefs or concerns about the meaning of their symptoms, based on folk knowledge, lay literature, or experiences with friends and family.[26] Asking about these is important because patients will be unable to listen to new information until they feel that they have been heard and understood. Ask patients what they think is wrong: "Most patients already have some ideas about what could be wrong. What thoughts or concerns have you had?" Patients may respond with new information: "They told my brother it was just a cold, but it was really pneumonia. He wound up on a breathing machine." Before examining patients, ask "What would you like me to pay particular attention to?" Ask patients what they think should be done for them: "What have you already tried? What else do you need?" Asking patients what others have said about the problem can also help reveal hidden concerns.[27] Most patients have an informal health advisor—often a family member, friend, or neighbor—who has suggested possible diagnoses or treatments. Finally, patients who change from fee-for-service to managed care may find that tests and treatments that were provided without question are now viewed as misguided requests.

A next step is to find ways to work with patients when their assessments and plans conflict with your own.[28,29] Acknowledge that a disagreement exists: "We seem to be disagreeing about whether you need antibiotics to get over this cold," but remain open to caring for the patient within your limits: "If you feel that you can work with me despite this disagreement, I'd still like to be your doctor and help you manage your health." Empathize with the patient's dilemma: "I can see this hasn't worked out at all like you wanted. No wonder you're frustrated." Provide a rationale for your decision: "The group of doctors I work with have reviewed the medical literature on this topic, and we all agree that there is no proven benefit of antibiotics for this condition." Consider sharing decision-making responsibility with the patient: "The chance that this is bacterial is about the same chance of your getting a side effect from an antibiotic. How do you think we should proceed?" Reaffirm the goals of the visit, which can sometimes be met more appropriately through other means (for example, in the case above, with a note to the employer or a phone call to the spouse). Physicians may reasonably choose to prescribe antibiotics in this case and save negotiations for larger issues: "I have a terrible sinus headache with this cold. I brought in this clipping about CT scans of the sinuses in people with colds. I'm covered for that, aren't I?" At times a mutually agreeable solution cannot be found, leaving both parties dissatisfied.

You Fix It Now

"You're not going to be happy with me today. This darn diabetes is just going crazy. The sugar is always up no matter what I eat or do. I wish you doctors could find some way to control it."

This patient seems puzzled by her diabetes mellitus, as though it has a life of its own. Although the condition is chronic, incurable, and best managed by the patient herself, she seems to want a "quick fix" by her physician. Because of the extra time and energy involved in communicating with her, she represents a financial risk in a capitated health care plan, where the primary physician receives a fixed amount for her care. Rather than become angry and frustrated with such patients, consider using empathy: "I can see that this diabetes is really a struggle for you. You'd really like us to take care of it for you, like a broken bone. But you're finding that diabetes isn't like that. It requires a lot of work on your part. I'll bet that's really disappointing." This statement goes beyond empathy by making clear to the patient that she has responsibilities as well as rights in receiving safe and effective health care.

The next step is to find out what keeps her coming to the physician. What goals or gains does she hope for—to feel better? to avoid heart attacks? or to appease her family? Exploring these goals takes some time but demonstrates to her that her ideas and participation are

important. Clarifying her goals can lead to a discussion of what she already knows about her diabetes, what she is ready to do differently, and what she needs next to change her behavior.[30] Once goals are established, strategies to reach them become clearer: "If our goal is to reduce your risk of blindness, your job is to keep a blood sugar diary, and my job is to advise you on how much food, exercise, and insulin to take." A patient's noncompliance can be put into the context of a normal response: "Many of my diabetic patients have trouble keeping track of food and blood sugars. What trouble have you had?" and then explored: "What else could you do to remember to take your blood sugar when you first get up?" Noncompliance can be presented as a choice that rests with the patient: "You've told me that you really enjoy smoking and don't want to stop. But you also worry that smoking increases your risk for another heart attack. How is this a problem for you?"[31] For patients with many problems—for example, obesity, diabetes, hypertension, and hyperlipidemia—small, incremental changes toward one goal at a time are most likely to be successful.[32]

Seeing the Specialist

"I know how my insurance works. If you don't send me to the gynecologist, then you get to keep the money. But the one who took out my cancer said I should see him every 3 months. He really understood my care."

This patient's previous gynecologist is not a member of her new managed care plan. In her new plan, the primary physician receives a fixed amount for her care, from which expert consultant expenses are deducted. The continuity relationship she enjoyed with her previous gynecologist is gone, her new physician is cost-conscious, and she feels cheated and abandoned.

An early goal for the physician in this visit is to keep the focus on the provision of quality health care rather than on the managed care plan. Address the patient's feelings of loss and frustration, but explain her current plan in realistic, unbiased terms: "I can understand how upsetting it must be to have your previous care interrupted. On the other hand, you've got a good plan. It allows you good medical care, but it restricts the use of specialists. It requires that I do things for you that we normally do in the office, such as pelvic exams and Pap smears. If something comes up that you and I decide needs the input of a specialist, I'll help you get it."

The patient's ability to trust her new physician can also be dealt with explicitly: "It sounds as though you're not sure I'll have the knowledge or skills to take care of you properly, or worse, that I wouldn't act in your best interests. I want you to know that my goal, like yours, is to provide the very best care we can. If at some point you feel that we're not meeting that goal, I hope we can talk about it and reach a solution together." Then do a thorough and careful examination as evidence of your competence and concern.

As managed care plans expand, referral patterns between primary care and specialist physicians can change rapidly. Primary care physicians help specialists by formulating specific questions and defining roles and tasks for follow-up. Specialists can help by being brief and specific, anticipating problems, and identifying contingency plans.[33] Specialists may also wish to identify the primary physician as the patient's "point of contact" for follow-up. This approach is challenging in highly technical specialties—for example, cardiac electrophysiology—where standards of care are constantly being revised.[34]

Bending the Rules

"Doc, I haven't seen a dentist in years, and I can't afford to now. Could you make a referral saying that I need it because of my diabetes? Then the plan will pay for it."

In some managed care plans, coverage for certain types of care, such as dental, optometric, preventive, or mental health, is minimal or absent depending on the level of coverage purchased. Physicians working in such plans should be familiar with the types of care that are covered and denied, what specialists are available and their qualifications, and the physician's role if specialty treatment is denied by the plan.

This physician has a number of options, reflecting his or her various roles. Administratively, he or she can refer the patient to an eligibility office, write in support of the patient's request, or ensure that the eligibility committee has appropriate input from both patient and physician. Clinically, the physician can request specialty consultation to evaluate the effect of the dental condition on diabetes—for example, "rule out dental infection." Investigators found that physicians are willing to use deception in recording the reason for ordering a mammogram in a setting where mammograms ordered for "screening" are denied but those ordered to "rule out breast cancer" are approved.[35] Ethically, a physician's duty to advocate for the individual patient conflicts with his or her duty to work within the guidelines of the plan, which provides cost-effective care of a population of patients. Current ethical guidelines clearly support the physician's role as an advocate for individual patients.[36,37] Legally, if a plan denies care that a physician strongly feels is indicated, he or she may have an obligation to contest or appeal the decision on the patient's behalf and to discuss all options with the patient, including getting care outside the plan at the patient's expense. Although managed care plans may be held liable for a physician's actions, courts may also hold physicians responsible for upholding community standards of treatment, even when denied by a patient's plan.[38,39]

In responding to patients' requests to bend the rules, physicians' actions—and related communications with patients—can be impulsive, depending on their feelings about the individual patient, the ease of dealing with the managed care plan, and the time available to think about it. Such requests rarely require immediate action. Physicians should take time to consider the issues just outlined, their personal responses to them, and what messages they want to convey to their patients. Then

they should communicate the message clearly: "I'd like to help you, but I don't think your teeth are aggravating your diabetes, and I'm not comfortable bending the rules that way."

How Managed Care Organizations Can Facilitate Physician-Patient Communication

Managed care plans can help physicians and patients communicate more effectively. For patients, the plan can describe what to expect regarding time with a physician, use of the telephone and emergency room, and the roles of other health care professionals in enhancing physician-patient communication. The plan can also describe policies regarding referrals to specialists, handling of grievances, and physicians' role as patient advocates if financial conflicts of interest arise. For physicians, the plan can provide opportunities to review how its promises and limitations are marketed to possible subscribers and its development of resource allocation guidelines to avoid "bedside rationing" by physicians.[36] Programs should be available to educate and coach patients in the management of common health problems and to educate providers in population-based and traditional dyadic medical care.[40]

Second, there should be a well-defined, physician-generated, prospective internal policy for dealing with difficult physician-patient relationships, including a means for terminating a patient's relationship with an individual provider or with the entire plan.

There should also be a strong, sensitive central administrative physician to deal directly with patients who have insistent demands and contentious behaviors. This frees up primary care professionals to be advocates for good medical care and to negotiate about medical rather than administrative issues.[9] Some administrators and risk managers unwittingly undermine physicians' efforts to provide safe, effective health care when it involves setting limits on patient demands, by tracking patient complaints as the only relevant outcomes, or by administratively reversing physicians' decisions regarding patients' requests. Managed care plans may reasonably decide that for some patients unable to cooperate with their physicians in obtaining safe, effective care, disenrollment is administratively preferable to providing substandard care.[9,41]

Finally, managed care plans should provide training in physician-patient communication. Plan administrators and risk managers should work collaboratively with physicians to identify mutual goals for such training and to ensure that the plan's policies and measures of quality of care support those goals. Goals for administrators and risk managers could include greater patient satisfaction and retention and fewer complaints or lawsuits. Goals for physicians could include fewer frustrating patient encounters, improved treatment adherence, and improved job satisfaction. All of these outcomes are demonstrably related to physicians' communication skills. Skills training is best conducted in workshop format, with opportunities to review recent research findings in physician-patient communication, practice new skills in relevant and realistic situations, and work in small groups with a free exchange of ideas and feedback. Such training is increasingly part of medical school, residency, and continuing education curricula.[42-44]

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Articles

Primary Care Physicians in Underserved Areas
Family Physicians Dominate

WILLIAM H. BURNETT, MA, *Irvine, California*; DAVID H. MARK, MD, MPH; JOHN E. MIDTLING, MD, MS; *and* B. BRUCE ZELLNER, MA, *Milwaukee, Wisconsin*

Using the definitions of "medically underserved areas" developed by the California Health Manpower Policy Commission and data on physician location derived from a survey of California physicians applying for licensure or relicensure between 1984 and 1986, we examined the extent to which different kinds of primary care physicians located in underserved areas. Among physicians completing postgraduate medical education after 1974, board-certified family physicians were 3 times more likely to locate in medically underserved rural communities than were other primary care physicians. Non–board-certified family and general physicians were 1.6 times more likely than other non–board-certified primary care physicians to locate in rural underserved areas. Family and general practice physicians also showed a slightly greater likelihood than other primary care physicians of being located in urban underserved areas.

(Burnett WH, Mark DH, Midtling JE, Zellner BB: Primary care physicians in underserved areas—Family physicians dominate. West J Med 1995; 163:532-536)

For more than two decades, public policy has promoted programs designed to establish the medical specialty of family practice. Two assumptions underlie these policy initiatives: first, that there exists a geographic maldistribution of physicians, and, second, that physician residency programs organized in specific ways can prepare physicians for practice in communities that lack the full range of medical services available in affluent urban areas.

The idea of geographic maldistribution further implies that specific geographic areas—usually rural or inner city—exist that are relatively deficient in primary care physicians and possibly other medical resources as well. Little research has been done to examine these assumptions in detail, in part because researchers have lacked the tools to delineate medically underserved areas with sufficient precision.

Specifically, a few studies have been done comparing the extent to which graduates of family practice, internal medicine, general pediatrics, and other primary and non-primary care residency programs locate in more rural areas or areas of lower physician density.[1-3] When family practice residency graduates have been compared with other primary and non-primary care residency graduates, they have been found to have a greater likelihood of choosing a rural practice site. Not all rural areas are necessarily medically underserved, however, and none of these studies considered urban underserved areas.

Studies concerning the extent to which graduates of family practice residency programs have alleviated geographic maldistribution with respect to explicitly defined underserved areas have been limited to small numbers of family practice graduates, typically from a single institution, or a relatively brief time after graduation from the residency and without making comparisons with other types of physicians.[4-9]

The State of California developed two data sources that allowed us to avoid the drawbacks faced by previous studies of not having explicitly defined rural and urban underserved areas or a large number of physicians, most of whom have been practicing for several years. The objective of this study was to use these data to measure the relative extent to which different types of primary care residency programs are contributing to solving the physician maldistribution problem.

Physicians and Methods

The State of California licenses physicians for a two-year period. Renewal periods are staggered so that an average of 4% of all California licensees must apply for renewal each month. During the period July 1984 through June 1986, the state required all physicians renewing their California license to answer a questionnaire. A questionnaire was sent to only those physicians applying for relicensure. Omitting first-time applicants for licensure reduced the proportion of respondents who might still be serving their residency. Any relicensure

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ABBREVIATIONS USED IN TEXT

HPSA = health professional shortage area
MSSA = medical service study area

applicants who did not fill out the questionnaire had their application returned to them,[10] thus ensuring a 100% response rate. There were 77,761 respondents, 50,677 of whom reported being in practice or employed in California. Our study further restricted itself to examining the practice location of physicians who completed their postgraduate education after 1974. Of the 50,677 California physicians, 20,275 physicians had done so.

The questionnaire required physicians to indicate their specialty, whether they were board certified, the date of last postgraduate training, and practice location. The questionnaire required respondents to choose one specialty from an accompanying list. Of the 20,275 physicians, 8,345 indicated their specialty as either family or general practice, obstetrics and gynecology, internal medicine, or pediatrics. These physicians constituted the group that we examined in this study. Because the first family practice residency was approved in 1968, only a small number of family physicians would be residency-trained before that date.

Among physicians with board certification, there ought not to be any general practitioners. A small percentage of general practitioners indicated they were board certified, however (3.6%). The percentage of obstetricians and gynecologists who indicated they were gynecologists only (rather than both) was also small: 9.6%. The findings proved virtually the same whether or not these two groups were included in the analysis. We included them in the data presented in this study.

By California statutes, the California Health Manpower Policy Commission is required to determine which areas of the state are medically underserved. The commission developed its own method of defining underserved areas, rather than using the federally designated Health Professional Shortage Area (HPSA) definition. The commission's determination of which areas were medically underserved involved a process that combined a "rules"-based approach and political and administrative judgment. The rules approach began with census county divisions as the units of analysis. These were aggregated into "medical service study areas" (MSSAs). Medical service study areas were constructed by aggregating census county divisions that were within 20 mi of a principal population center. Census county divisions outside the 20-mi perimeter of population centers were left desegregated—each making up an MSSA. Medical service study areas were designated as "rural" if the population density was less than 250 persons per sq mi and contained no incorporated community with more than 20,000 population. They were designated as "urban" if either of these criteria did not hold. Urban MSSAs with more than 40,000 population were, in many cases—and in all cases of larger cities—further subdivided into smaller MSSAs after consulting with local health departments. The commission then invited and responded to specific criticisms of this process and the resulting MSSA geographic pattern. The ultimate objective of the commission was to define areas in which the number of physicians practicing in the area determined the access to physician services of area residents. The result was the division of the state into 453 MSSAs, based largely on rules, but especially in urban areas, allowing judgment to influence MSSA boundaries.[11,12]

All relicensure applicants had to indicate their primary practice location, including zip code, on the questionnaire. The zip code of the primary practice location was used to assign physicians to MSSAs.

The population of each MSSA was then divided by the number of primary care physicians practicing in the MSSA, as determined by the licensure questionnaire. If the ratio was greater than 1,966 persons per physician, the MSSA was designated as underserved. This level is 175% of the statewide average of 1,123 persons per physician. A lower ratio of 1,855 (165% of the statewide average) was used to designate an MSSA as underserved if the percentage of the population younger than 5 years exceeded 5.5%, that older than 64 years exceeded 22.5%, or the percentage of the population with family income under the US poverty line exceeded 20%. This process was completed during 1984. There were 254 urban MSSAs, and of these, 120 (containing 41% of the urban population) were designated as underserved. There were 199 rural MSSAs, of which 158 (containing 73% of the rural population) were designated as underserved.

We tested the null hypothesis that each specialty's physicians were distributed across urban and rural underserved MSSAs in the same way as physicians in the other three specialties. We used *t* tests for the difference in proportions, comparing the proportion of physicians in each of the four specialties located in a rural underserved area with that of physicians in the other three specialties located in rural underserved areas. The same procedure was then repeated for urban underserved areas. The same steps were followed for analyzing the data for non–board-certified physicians. We treated board-certified physicians and non–board-certified physicians separately because we thought it possible that the non–board-certified physicians, as a group, contained a higher proportion of physicians who had not completed an approved residency program and that this might affect location patterns. The differences in the location pattern between board-certified and non–board-certified physicians within a primary care specialty were tested with the *t* test for the differences between two sample proportions.

In reporting the results, we give the *P* value of the two-sided *t* test, which is the probability of observing the absolute value of the difference in the proportions we obtained, or an absolutely greater value, if the null hypothesis were true—that is, the true difference in proportions is 0. The *P* values were determined using the Microsoft Excel, version 5.0, program.

TABLE 1.—*Percentage and Number of Each Type of Board-Certified Primary Care Physicians Located in Adequately Served, Rural Underserved, and Urban Underserved Areas*

	Board-Certified Primary Care Physicians							
	Located in Adequately Served MSSAs,		Located in Underserved Rural MSSAs,		Located in Underserved Urban MSSAs,		Total,	
Specialty	%	(No.)	%	(No.)	%	(No.)	%	(No.)
Family and general practice	57.0	(693)	15.1	(184)	27.9	(339)	100	(1,216)
Obstetrics and gynecology	72.7	(453)	5.6	(35)	21.7	(135)	100	(623)
Internal medicine	74.5	(1,796)	4.9	(118)	20.7	(498)	100	(2,412)
Pediatrics	74.1	(709)	4.7	(45)	21.2	(203)	100	(957)
Total primary care other than family practice	74.1	(2,958)	5.0	(198)	20.9	(836)	100	(3,992)
Total primary care	70.1	(3,651)	7.3	(382)	22.6	(1,175)	100	(5,208)

MSSAs = medical service study areas

Results

Table 1 shows the percentages and number of board-certified physicians in total, with family practice physicians excluded from the total, and in each of four primary care specialties located in rural and urban medically underserved MSSAs and adequately served MSSAs. The data in the table indicate that board-certified family practice physicians are substantially more likely than other primary care specialists to be located in underserved areas.

The probability of a board-certified family practice physician locating in a rural underserved area is three times greater than that of other, non–family practice, board-certified primary care physicians as a group (15.1% verses 5.0%, $P < .0001$). The probability of family practice physicians locating in an urban underserved area is 1.33 times greater than that of other primary care physicians. Although this is a lower ratio than in the case of rural underserved areas, it is still statistically significant ($P < .0001$).

The percentages of board-certified family practice physicians located in urban and in rural underserved areas (15.1% and 27.8%, respectively) are insignificantly different from those found in another study done in Fresno, California (13% and 33%, respectively).[9] The sample of physicians in that study consisted of 126 graduates of California family practice residency programs two to five years after graduation.

Table 2 shows the proportion and number of non-board-certified physicians in each of four primary care specialties located in medically underserved MSSAs. Family and general practice physicians still have a significantly greater percentage of being located in underserved areas than do other primary care physicians ($P < .001$ for rural and $P < .04$ for urban underserved areas).

Comparing Tables 1 and 2, the percentage of all non–board-certified family and general physicians located in rural underserved areas is only 7.2%, which is less than half the 15.1% for those who were board certified ($P < .0001$). The percentage of other non–board-certified primary care physicians located in rural underserved areas (4.4%) is also lower than it is for those with board certification (5.0%), but only slightly and insignificantly lower ($P > .3$).

TABLE 2.—*Percentage and Number of Each Type of Non–Board-Certified Primary Care Physicians Located in Adequately Served, Rural Underserved, and Urban Underserved Areas*

	Non–Board-Certified Physicians							
	Located in Adequately Served MSSAs,		Located in Underserved Rural MSSAs,		Located in Underserved Urban MSSAs,		Total,	
Specialty	%	(No.)	%	(No.)	%	(No.)	%	(No.)
Family and general practice	64.5	(741)	7.2	(83)	28.2	(324)	100	(1,148)
Obstetrics and gynecology	72.7	(405)	5.3	(30)	22.6	(127)	100	(562)
Internal medicine	70.1	(610)	4.4	(38)	25.5	(222)	100	(870)
Pediatrics	70.4	(392)	3.4	(19)	26.2	(146)	100	(557)
Total primary care other than family practice	70.7	(1,407)	4.4	(87)	24.9	(495)	100	(1,989)
Total primary care	68.4	(2,148)	5.4	(170)	22.6	(819)	100	(3,137)

MSSAs = medical service study areas

With respect to urban underserved areas, non–board-certified physicians have higher percentages located there. For family physicians, comparing Tables 1 and 2, the percentages of certified and non-certified physicians located in urban underserved areas are 27.9% and 28.2%, respectively. This is not significant ($P > .85$). For obstetrics and gynecology, internal medicine, and pediatrics taken together, the percentages of certified and non-certified physicians located in urban underserved areas are 20.9% and 24.9%, respectively. Although this is a significant difference ($P < .001$), most of the difference is due to internists and pediatricians. Board-certified and non–board-certified obstetricians and gynecologists have nearly the same percentage practicing in urban underserved areas (21.7% and 22.6%, respectively). The differences between board-certified and non–board-certified internists and pediatricians in the percentage practicing in underserved areas are 20.7% versus 25.5%, respectively, for internists and 21.2% versus 26.2% for pediatricians.

Discussion

The method of designating medically underserved areas used in this study differs markedly from that used for the federally designated HPSAs. There may be a strong selection bias determining which areas are designated HPSAs. The HPSA designation is made in response to an application by a person or organization in the area—often a clinic, hospital, or local public health agency. This requires investing considerable time and effort. Without this local initiative, no designation is made. Underserved areas that do not already have a local, stable, resourceful, and motivated health care organization of some type are not likely to be designated as HPSAs. Furthermore, the main requirement to be designated an HPSA is that the ratio of population to primary care physicians be greater than 3,500. From a political perspective, this is too extreme a value as a criterion for addressing inequities in access to primary care.

What explanations can be offered for the greater percentage of family physicians practicing in the designated underserved areas? First, there may be a specialty effect. Family physicians have a more general skill set than obstetrician-gynecologists, pediatricians, or internists. This implies that each family or general practice physician needs a smaller population base to provide a sufficient patient load than do the other primary care specialties. This could be a factor in explaining the relatively greater percentage of family practice physicians in rural underserved areas. Second, there may be a training effect. Family practice residency programs often are structured specifically to prepare physicians for direct patient care in ambulatory settings in communities for which there are access barriers (geographic, social, or economic) to non-primary care specialists and tertiary care services. Third, there may be a selection effect. Family practice residencies may attract young people who wish to locate in underserved areas, some of whom would have located in such areas even if they had had to choose a residency in some other primary care specialty. Family practice residency programs often deliberately recruit residents who are thought to be predisposed to practice in communities with a shortage of physicians.

Although family practice physicians have located in underserved areas in greater proportions than other primary care specialties, the differences are less dramatic for urban areas. Two possible reasons for this are as follows: the larger population base in urban underserved areas removes the advantage of the lower population base required by family and general practice physicians relative to the other primary care specialists, and there is a greater likelihood of error in designating urban areas as underserved. A physician located on a bus route a quarter mile outside an inner-city neighborhood may be serving that neighborhood but not be counted in calculating its population-to-physician ratio. Conversely, a physician may have a location bordering a downtown business district and the edge of an inner-city neighborhood. The physician may not treat many inner-city residents, but may be counted in the denominator of the neighborhood's population-to-physician ratio. Drawing the boundary of the inner-city neighborhood a few blocks in either direction can determine the frequency of each of these types of errors. Clearly, this type of situation is less likely to arise in rural areas. In any event, overestimating or underestimating the number of MSSAs that are actually underserved (nondifferential misclassification) makes it less likely that we will obtain significant differences among the four primary care specialties in their distribution between underserved and adequately served areas, when in fact true differences exist.[13(p86)]

Conclusion

Do family practice residency programs produce physicians who serve as the primary physician in underserved areas? The answer is a "relative" yes. Compared with other primary care specialties, family practice physicians have shown a greater willingness to locate in underserved areas, both rural and urban. We cannot in this study clearly distinguish between the specialty, training, or selection effects, however, or measure their relative importance. It seems likely that the percentage of family practice physicians who completed an approved residency program is higher for those who were board certified, relative to non-board certified. To the extent that this may be the case, the greater percentage of board-certified family practice physicians located in rural underserved areas points to the existence of a training effect. It may be possible to include the specific features of family practice residency programs that comprise the training effect, if they can be identified, in other primary care residency programs.

Many pediatricians, internists, and obstetrician-gynecologists have chosen to locate their practices in underserved areas, and together these physicians make up the majority of primary care physicians in underserved areas (71%). Whatever accounts for the higher percentage of family practice physicians locating in

underserved areas, it is clearly a question of degree, rather than an absolute distinction.

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* * *

The Thank You Note

We went to See's Candy.
She picked
the biggest box.
On the note
she wrote, "To all the great nurses!"
and looked at me for approval.
I read what that tiny card really said.
"To all the great nurses,
not the bossy one,
not the one who left two stitches in me,
not the one who ripped the bandage off. 'Ouch'
No. To all the great nurses,
the funny one
who had long conversations
with the IV machine,
big fat chocolates to her.
The night nurse who tried to be so quiet,
the nurse who brought
the two-day-old baby
from the next room
all wrapped up
for me to see,
to all the great nurses
who never made me feel
I was their job,
to the so-patient nurses
who explained what they were doing.
To all the great nurses!
Thanks."

ARLYN SERBER©
Sausalito, California

Articles

A Homeless Shelter Medical Clinic Organized and Staffed by Family Practice Residents

DAVID C. FIORE, MD, *Reno, Nevada*

A medical clinic was organized in a homeless shelter to help address the health care needs of the homeless population in a small California city. A second-year family practice resident, together with two community nurses and a local family practitioner, organized and staffed the clinic. After the first winter of operation, family practice residents on their own initiative took over the management of the clinic. The clinic serves the needs of the clients in the homeless shelter, provides family practice residents an opportunity to work independently of the residency program, and offers a sought-after experience in caring for the underserved.

(Fiore DC: A homeless shelter medical clinic organized and staffed by family practice residents. West J Med 1995; 163:537-540)

Homelessness in America is, unfortunately, a growing problem. Recent estimates of the homeless population range from 350,000 to 600,000, with families identified as the fastest growing homeless group (*CQ Researcher*, August 7, 1992, p 675).[1,2] Although many communities have developed emergency shelters to provide temporary housing, many of the people using these shelters are in poor health or at the very least lack ongoing health care and frequently use emergency departments as their only contact with the health care community. The Stewart B. McKinney Homeless Assistance Act of 1987, which mandated funds to provide primary care to homeless persons, represents an attempt to meet the challenge of providing health care to this population on a national level. In many communities, however, volunteer efforts were undertaken to meet the medical needs of the homeless.[3]

Medical Problems of Homeless Persons

Although homeless people suffer all the illnesses of domiciled persons, they are also at much higher risk for many medical problems. Some of these problems stem from self-selected behaviors, including tobacco and illegal drug use. Current or past drug abuse was reported by 85% of the men and 67% of the women in one homeless shelter.[4] In Atlanta, Georgia, the average age of death for homeless persons was 46 years, with nearly half of the deaths attributed to acute or chronic effects of alcohol abuse.[5] Homeless persons also appear to suffer from chronic illnesses at a much higher rate than the general public, with 40% to 75% of homeless reporting chronic health problems.[6,7] In larger cities, the spread of tuberculosis among homeless persons has become almost epidemic. This problem is compounded by the close living quarters in many of the shelters and the difficulty in ensuring that infected persons comply with their therapy.[8,9] Another epidemic that affects homeless persons more frequently than the domiciled is that of accidents and violence. In one study, 40% of homeless persons reported suffering an accident in the previous two months, and in a study from Georgia, 42% of deaths in homeless persons were due to accidents or violence.[5,6]

Families and children appear to suffer inordinately in the homeless environment. A study of homeless families revealed that the overwhelming proportion of them are headed by a single unemployed woman with minimal support, many with compounding mental health and substance abuse problems.[10] Children in the homeless environment have chronic illness at twice the rate of the general population, trail in immunizations, and are developmentally delayed at an alarming rate.[10-12] The greatest threat to the well-being of homeless children and adolescents may be psychosocial development. Homeless adolescents are often fleeing a hostile home environment, one in which they may have suffered abuse and neglect.[13] Numerous studies have shown that homeless children have a higher frequency of behavior problems (particularly antisocial behavior) than domiciled children and report a much higher incidence of depressive symptoms and ideation.[13-15]

Redding, California, Demographics

Redding is a city of about 66,000 at the northern end of the Sacramento Valley of California. It developed as, and still is, a major rest stop for travelers heading up and down the valley. In 1989 the unemployment rate averaged approximately 9.2%, and about 9,000 families or persons were receiving government assistance.[16]

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Redding Armory Homeless Shelter and Medical Clinic

To assist homeless persons in the city of Redding, the Salvation Army and People of Progress joined forces in 1988 to set up a shelter to operate during the winter months. Impromptu health care stations were set up on a sporadic basis in the latter part of the first season. In the fall of 1989, a second-year family practice resident collaborated with the nurses and physician who had previously provided services to the shelter. To provide some continuity of care, they arranged to operate a clinic on a weekly basis.

For the first year of operation, the clinic was staffed by one resident and one practicing family physician, two nurses, and, when possible, a social worker and a mental health worker. On-site medications were kept to a minimum, with the intent to refer most ongoing health problems to appropriate resources. Experience from the previous year had indicated that most of the homeless clients were eligible for one of three health systems that served the indigent population: Shasta County Clinic, Department of Veterans Affairs, or Indian Health Services. These services were substantially underused, however, with most homeless persons visiting emergency departments as their only contact with health care providers. Backup radiology and laboratory evaluations were done, free of charge, by the resident's hospital, with professional fees waived by the respective departments. A prescription charge account was set up at a local pharmacy through funds donated by the Redding Rotary Club.

The dual goals of the clinic organizers were to provide health care services to persons who had inadequate primary care and to familiarize family practice residents with the health care problems of homeless persons. One of the major impediments to recruiting physicians to work in indigent and homeless care settings is overcoming physician biases and fears.[3] By providing residents a positive experience in a homeless shelter, the organizers believed that these biases and fears could be alleviated.

Methods

Client use and demographic data for the shelter were recorded and compiled by shelter staff personnel from the Salvation Army. Clinic use was recorded by volunteer medical records personnel. Brief medical records were kept on all clients seen in the clinic, with the recording of name, complaint, diagnosis, treatment, and referral, if indicated. Family status was recorded on all patients. Data were entered in a computer database for sorting and analysis.

TABLE 1.—*Demographics of Homeless Shelter (n = 663) and Medical Clinic (n = 183) Clients*

Demographics	*Homeless Shelter, No. (%)*	*Medicol Clinic, No. (%)*
White	609 (92)	150 (87)
Hispanic	20 (3)	20 (5)
Black	14 (2)	4 (2)
Native American	19 (3)	9 (5)
Asian	1 (0.2)	0 (0)
Veteran	177 (27)	40 (23)
County resident	229 (35)	69 (40)
Nonresident	434 (65)	114 (60)

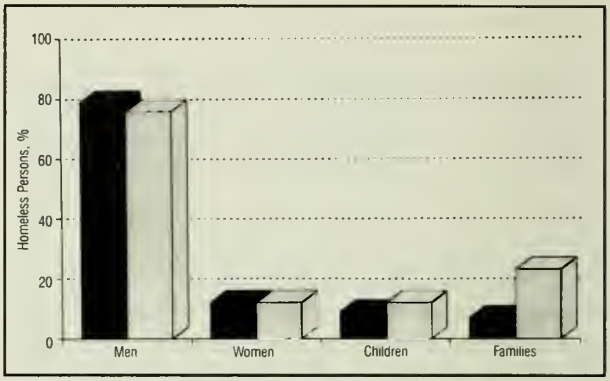

Figure 1.—The graph shows a breakdown of the homeless shelter (■) (n = 663) and medical clinic (□) (n = 183) clients by families, men, women, and children.

Outcome

During the 1989-1990 winter season (December through March), the shelter was open for 113 nights and lodged 663 persons; there was an average of 63 clients per night, for a total of 7,098 lodgings provided. The shelter demographics were similar to those of other shelters, with men (especially veterans) overrepresented (Table 1).[17,18] Use of the clinic was proportionally higher for children and families, however, than it was for single men (Figure 1).

During this period, the clinic saw 278 clients and dispensed 205 medications (to 160 clients). Upper respiratory tract infection, skin problems, and pharyngitis accounted for almost a third of the visits. Hypertension and chronic obstructive pulmonary disease (COPD) accounted for another 10% of visits (Figure 2). Of 186 referrals made, only 1 was to an emergency department. The rest of the referrals were to either the Medi-Cal office (California's Medicare), Indian Health Services, or Veterans Affairs clinics.

Discussion

Medical Issues

The homeless persons served by this clinic appeared to be in better health than those in studies done in major cities.[2,4,19] The clients did, however, have a notably high rate of chronic disease, such as COPD and hypertension, that frequently was untreated. One of the primary goals of this clinic was to assist the clients of the shelter in taking care of their health needs by referring them to the appropriate medical resource. The success in meeting this goal is reflected by the high referral rate to the coun-

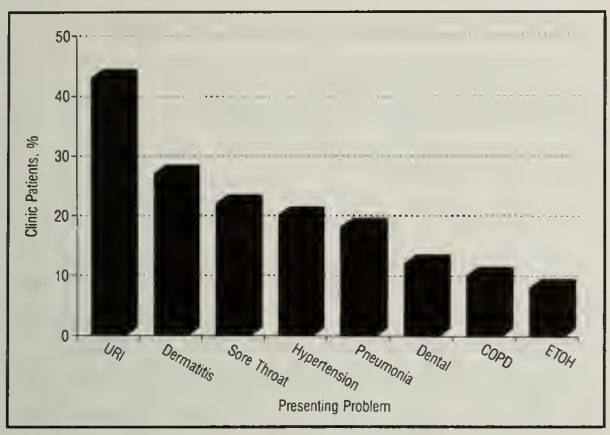

Figure 2.—The graph shows the presenting problems of patients seen at the medical clinic (n = 183). COPD = chronic obstructive pulmonary disease, ETOH = ethyl alcohol [alcohol-related disorders], URI = upper respiratory [tract] infection

ty's indigent clinics, with only one referral to an emergency department.

Although official data are unavailable, conversations with physicians and directors of the two emergency departments in Redding suggest that there has been a decreased use of the emergency departments by homeless persons since the clinic started operation.

Educational Issues

Studies on the integration of a homeless shelter experience into family practice residencies have reported increased awareness of the problems facing homeless persons and increased comfort in dealing with this population.[20-22] In one study it was found that as little as half a day of working in a homeless shelter substantially improved the residents' understanding of the causes and implications of homelessness.[22] In 1990, a pilot education and research elective was developed for residents and students working in a homeless shelter.[23] Consistent with the Redding experience, it was reported that residents rated the elective positively and that requests for the elective quickly outpaced availability.

Whereas the clinic experience has been well received by the family practice residents, it has not been without difficulties. Many shelter patients have complex medical histories that initially seemed overwhelming to some of the residents. Although most of the residents welcomed the opportunity to work independently from the residency program, this, too, was intimidating to a few of them. There were also difficulties in the care of some of the patients, especially with compliance. We were able to improve compliance as we became more familiar with some of the difficulties facing homeless persons—lack of money and transportation, unstructured lifestyle, poor social support.

In 1995 the clinic continued to operate in a similar manner, with the second- and third-year residents volunteering to staff it on a rotating basis. In staffing the clinic, the residents do not gain any credit toward their residency requirements. Responsibility for organizing staffing and supplies for the clinic has also been taken over by one of the residents each year. In the years since the clinic has become a "resident project," nearly every resident who has graduated from the family practice program has worked at least one shift in the clinic. In fact, residents have found it difficult to get scheduled as the "Shelter Doc" unless they volunteer early. They say that they value the unique experience of working with a difficult group of patients with complex psychosocial issues in the clients' own, rather than the physician's, environment.

The residency administration decided to continue supporting the shelter clinic without formally incorporating it into the residency program. This policy has allowed the residency to include coverage of the shelter clinic in its malpractice insurance, while maintaining the clinic's truly volunteer nature. It has been continued as a "residents' project" rather than a "residency project." By adopting it as their own project, the residents have personally invested in the shelter clinic. This probably would not have occurred if it had become a required element of the residents' training. The project has also provided some of the residents the experience of being personally in charge of the organization and daily management of a fairly complex clinic. Most important, however, this policy has encouraged the residents not only to gain a valuable learning experience, but also to attain a sense of fulfillment that comes from performing charitable work with clients who clearly need their services. The residents look forward to working in the clinic, even though they get no time off from their already busy schedules and gain no official recognition for their time and effort at the clinic. Studies suggest that exposing students, and residents, to underserved populations such as the homeless increases their awareness of professional values such as altruism and equality.[24] This experience may help encourage the physicians who graduate from the program to continue to seek the joys that come from helping people who need it, without regard to compensation.

Acknowledgment

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* * *

The #1 Cause of Death

They are telling doctors how to ask
The right questions; to get to the truth
Beneath the clenched jaws, silence and bruises.
But what is the proper remedy?

Here, take two aspirins, and hide;
Take your children now to the shelter
Don't wait for more proof.
You will never be secure,
It will not go away;
He will kill you if you take it long enough.
You are the real Cinderella
The glass slipper fits;

Except there is something wrong with the prince—
Inside his mind the violence builds to explosions
Like atomic bombs in your life—
Your livingroom and your kitchen
Are full of land mines;
You are in a war zone
Weaponless and weeping
Oh, for the love of God and your children, Leave!
I write this as an Rx,
as your physician I order you—
As a mother I beg you,
Do not stop to feel defeated, just move,
Keep your feet on the path to the shelter,
Later, later, you can grieve.

MARTINA NICHOLSON©
Santa Cruz, California

Articles

What Physicians Should Know About Africanized Honeybees

RONALD A. SHERMAN, MD, MSc, DTM&H, *Irvine, California*

The Africanized honeybee, popularly known as the "killer bee," is already well established in Texas and has recently entered California and Arizona. As the Africanized honeybee spreads in North America, the medical community must become aware of the problems associated with this insect and ensure that sting emergencies can be handled quickly and appropriately. The major differences between Africanized and European honeybees are that the former are more irritable, they swarm more readily and frequently, they defend their hives more vehemently, and they sting more collectively. It is not the composition nor the volume of an individual bee's venom, but rather the cumulative dose of multiple stings that accounts for the morbidity and mortality associated with Africanized honeybee-sting incidents. Even nonallergic persons are susceptible to the toxic effects of these large combined venom loads. Africanized honeybee-sting victims are treated the same as victims of European honeybee stings. Authorities will prepare for the bees' arrival by expanding public awareness, teaching risk-avoidance behavior, providing for the removal of troublesome hives, and developing sting treatment protocols that can be initiated rapidly in the field or emergency departments. Health care professionals should participate in the educational efforts and in the development of needed emergency response protocols so that the effects of the Africanized honeybee will be merely a nuisance rather than a plague.

(Sherman RA: What physicians should know about Africanized honeybees. West J Med 1995; 163:541-546)

In many areas of the country, policy makers and the agriculture community are preparing for the arrival of the Africanized honeybee. Popularly (and inappropriately) known as the "killer bee," this insect entered Texas in 1990,[1] and it has now been identified in California and Arizona.[2,3] The limits of its northward expansion are thought by some experts to be the southern third of the United States,[4] but its ultimate limitations will depend on its ability over time to develop a tolerance to cold.

The medical community, too, should prepare for the continued spread of this insect, not because of some impending health crisis that will result from the influx of this aggressive bee, but because of the many questions, concerns, and fears that the public may have. Experience in South and Central America has shown the importance of public education, readily accessible emergency treatment, and a coordinated bee tracking and hive control program.[5] In adopting these principles in the United States, we may find that fatal stings resulting from this bee are relatively infrequent. Health care professionals can best prepare for the arrival of Africanized honeybees by understanding the nature of this bee, by ensuring that we can handle sting emergencies quickly and appropriately, and by participating in community education. To this end, it is hoped that an understanding of the material in this review will allow readers to answer the questions, and allay the fears, of their patients.

'Africanization' of Honeybees

Many races of honeybees exist today. Honeybees were brought to the New World by the European settlers.[6,7] European honeybees (*Apis mellifera mellifera*, *Apis mellifera ligustica*, *Apis mellifera carnica*, and *Apis mellifera iberica*) eventually established themselves throughout much of North and South America, with the exception of largely tropical regions. Reports of substantial honey production by the African honeybee (*Apis mellifera scutellata*) prompted several attempts to introduce this race into the Americas, but the bees never before survived as a distinct race.

In 1957, during studies of the African honeybee in Brazil, the queens and workers of 26 hives escaped into the countryside, establishing wild, or feral, African colonies.[8] The descendants of these bees are considered Africanized honeybees because they are actually a hybrid between these African honeybees and the local European honeybees. Many African traits have persisted despite the genetic mixing of races: excitability,

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aggressive defense of their hive, and frequent swarming. The Africanization process has spread north and south at a rate of 320 km (200 mi) per year, as these bees have continued to breed with, and often outcompete, the more docile European honeybees.[4]

The specific mechanisms of this hybridization, or Africanization, had long been unknown. Africanization could theoretically occur by the interbreeding of African drones with European queens or European drones with African queens. Recent findings of mostly African mitochondrial DNA (maternally inherited) imply that the territorial spread of the Africanized honeybee has occurred primarily as a consequence of female migration.[9,10] The accidental transportation of bees by humans, however, and parasitism of European honeybee hives by Africanized honeybees also play roles in the Africanization process.[6] The important issue is that the Africanized honeybee is a hybrid that has, for the most part, retained many of the aggressive behavioral traits of *A m scutellata*.

Natural History of African and Africanized Honeybees

The African bees' honey production may be greater than that of the European honeybees living in the same tropical regions.[11] It is not as enormous as many people once thought, however, nor is it even greater in all situations.[12,13] African colonies, like their Africanized descendants, produce a large number of workers that quickly leave the hive to forage independently and widely. These bees are well suited to environments where flowering plants are sparsely scattered and short-lived; they do not harvest large amounts of nectar, but they are well adapted to finding the available nectar when it is rare and dispersed.[14] Nectar is a major component of honey; pollen is the primary protein source for bee larvae. Compared with European honeybee colonies, more of the African (and Africanized) foraging force is engaged in collecting both nectar and pollen, rather than nectar alone.[11,15] This is not surprising, given that large brood production is a priority with the African and Africanized colonies.[11] European honeybees, on the other hand, through their dependence on dance communication and mass recruitment, are able to collect larger quantities of nectar when it is abundant.[12]

Some of the characteristics that make African honeybees better survivors in tropical Africa—frequent swarming, absconding in the face of adversity, and aggressive defense of the hive—have made Africanized honeybees a problem for beekeepers in the New World. When their colonies became Africanized, many South American beekeepers began to neglect their hive maintenance out of fear of being attacked.[5] This led to overcrowding, which increased the irritability of the bees. Overcrowded colonies would swarm to find more room, or completely absconded, leaving the old hive vacant. Swarming bees looking for a suitable site for establishing a new colony tend to be relatively docile. But when swarms settle in areas near people or livestock, then stinging episodes are likely to follow any disturbance of their new hive.

The architecture and site selection of Africanized honeybee hives differ from those of European beehives in that the Africanized hives are often more exposed.[15] Africanized honeybees often build their hives on tree branches or in old tires and boxes. These open nests are thus more likely to be disturbed by passersby, gardeners mowing their lawns, or environmental hazards, such as rain and wind.

Africanized honeybees are difficult to distinguish morphologically from European honeybees. Africanized honeybees are typically slightly smaller than most European honeybees. They can be identified by experienced entomologists on the basis of structure—relative wing, leg, and body measurements[16,17]—by gas chromatography of cuticular hydrocarbons,[18,19] or by enzyme electrophoresis.[20-24]

Africanized Honeybee Stings

The stinging behavior of Africanized honeybees is primarily one of defense. It is not an effective defense for an individual bee because the honeybee dies in the process of stinging vertebrates; but honeybee stinging is effective for group defense. Honeybees are capable of instilling large amounts of venom into a vertebrate victim as a result of their stinging mechanism, which continues to inject venom despite the death of the bee, and also as a result of colony recruitment into the attack.

Stings generally occur in the immediate vicinity of the hive, in response to a perceived threat.[25,26] The Africanized honeybee's notoriety (as well as its common name, killer bee) results from its aggressive defense of the colony.[27-29] Hundreds of people have lost their lives as a result of killer bee-sting incidents over the past few decades in South and Central America.[30] The sting and venom of the Africanized honeybee are not substantially different from those of the European bee[31,32] and are not themselves the cause of the high mortality.[33] Fatal Africanized honeybee-sting incidents tend to involve hundreds of individual stings. The same number of European honeybee stings would be expected to lead to similarly fatal outcomes.[34] It is the cumulative dose of venom injected by numerous Africanized honeybees that explains the higher morbidity of Africanized honeybee-stinging incidents, along with a greater likelihood of stinging a hypersensitive person, of course, when several people are attacked.

In general, honeybee stinging has been shown to be induced by sudden movements, dark colors, and certain odors, including human perspiration.[35] Honeybees also sting in response to volatile chemicals such as isoamyl acetate, released from the bee's glands at the time and site of each sting.[36-38] Through this mechanism, nearby honeybees are recruited in the attack and directed toward their victim. Africanized honeybees may be more sensitive to, or release greater quantities of, these recruiting pheromones.[39] Once initiated, the sequence of stinging recruitment in an African honeybee colony can result in

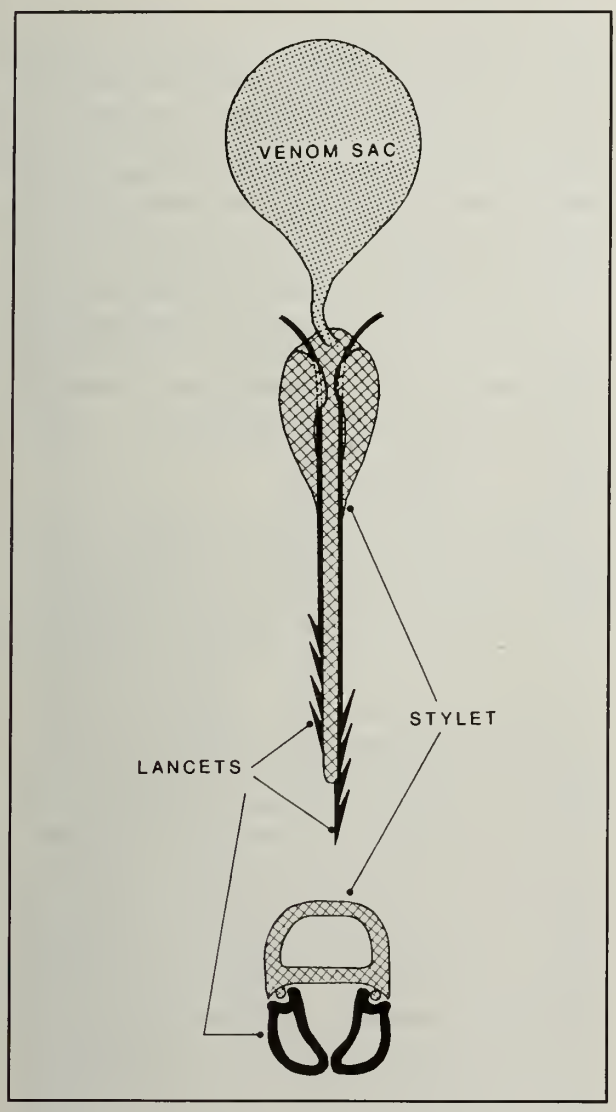

Figure 1.—The schematic drawing shows the honeybee-sting mechanism. The ventral view shows the alternating motion of lancets. The lower portion of the drawing shows a cross-section (based on Snodgrass[41] and Mulfinger et al[42]).

hundreds or thousands of individual stings.[28] These bees may pursue a victim as far as 1 km (0.6 mi) and may remain aggressive for hours or even days.[40]

The Sting

As for all honeybees, the sting mechanism (Figure 1) is composed of two barbed lancets tracking along a central stylet.[41,42] The alternating thrusts of the two lancets transport the sting farther into mammalian skin as each barbed lancet becomes firmly entrapped in the fibrous tissue, able only to advance and not retreat. As the lancets alternately advance, the venom is simultaneously pumped into the victim. When the honeybee attempts to escape, its barbed stinger will be left behind, still pushing forward and still pumping venom as a result of its self-contained venom sac and intrinsic musculature.

Honeybee venom comprises three categories of constituents (Table 1): enzymes, peptides, and biogenic amines.[43] The amount of venom in each Africanized honeybee venom sac may be slightly less than that of the European honeybees in the United States,[31] although the components are essentially the same.[32,44] Even within the same race, the dry weight of various venom components varies from one colony to another.[44]

Clinical Manifestations of Bee Stings

Few studies have looked specifically at the clinical manifestations of Africanized honeybee stings. Because the composition of their venom is essentially the same as that of European honeybees, the clinical manifestations are considered to be the same, adjusted for venom load (number of stings).

The reason that Africanized honeybee-sting incidents occasionally result in death is that they commonly involve hundreds of individual stings. The median lethal dose of honeybee venom has been estimated at 19 stings per kg, or 500 to 1,400 stings for humans.[45]

Although the clinical manifestations of Africanized honeybee stings have not been systematically studied, the spectrum of reactions to a single or a few European honeybee stings has been well described.[46] Honeybee-sting reactions are often classified as local, major local, or systemic; they can also be described as immediate or delayed. Local symptoms include pain, pruritus, erythema, urticaria, and angioedema. When severe but contiguous with the sting site, these symptoms are described as major local reactions. When these symptoms occur in remote locations, they are considered systemic reactions. Nausea, vomiting, diarrhea, and intestinal or uterine cramping are common systemic reactions. More severe systemic reactions include bronchospasm with wheezing, laryngeal edema with inspiratory stridor, dyspnea, hypotension, and a sense of impending doom. Hypotension or hypoxia may lead to a loss of consciousness. Bronchospasm or laryngeal edema can impede breathing, and cardiac collapse can cause shock; either one can be fatal.

The onset of some serious reactions can be delayed for 8 to 24 hours. Delayed renal failure has been described following Africanized and European honeybee stings.[47-51] Delayed hematologic[34,52] and neurolog-

TABLE 1.—*Major Constituents of Honeybee Venom Enzymes*

Enzymes	Mast cell-degranulating peptide
Phospholipase*	Secapin
Hyaluronidase*	Tertiapin
Acid phosphatase *	Protease inhibitor
α-D-Glucosidase	Biogenic amines
Lysophospholipase	Histamine
Peptides	Dopamine
Melittin*	Norepinephrine
Apamin	

*Allergens.

ic[47,49,52] complications have also been documented. The mechanisms of these complications are not yet completely understood.

Most of the deaths occurring in the United States are currently the result of anaphylaxis; these deaths often are associated with only one or two stings. More than 40 deaths are reported each year in the United States due to hymenopteran (ant, bee, and wasp) stings.[52] The true number of deaths is probably greater, given that some deaths that are attributed to cardiac arrests or to unknown causes may actually be the result of bee-sting anaphylaxis.[53,54] The prevalence of bee-sting allergy is estimated to be from 0.5% to 5%.[55-59] Most sting-related deaths in the United States now occur in older persons and in those with coronary artery disease.

Even a single bee sting to the neck, face, or mouth can cause substantial swelling and obstruct breathing.[60-62] Hundreds of stings, even in nonallergic persons, may lead to many of the manifestations seen in hypersensitive victims. Children are particularly susceptible to the effects of multiple stings because they receive a larger dose of venom per kilogram of body weight for any given number of stings. The proportion of children seriously injured in bee-sting incidents will probably increase as Africanized honeybee-stinging incidents become more common.

Psychological Aspects of Bee Stings

The tremendous psychological effects of the killer bee influx cannot be overemphasized. An uncontrollable fear of stinging insects is common.[63-65] Sensationalized reports of the Africanized honeybee, combined with myths about its lethal venom, enormous size, and ability to sting repeatedly, have created unwarranted anxiety.[65,66]

Most bee stings, at least for the next several years, will continue to result from European bees. Even when Africanized honeybee stings outnumber those of European honeybees, public fear must not be allowed to further complicate this already troublesome situation. If public fear escalates, the panic that ensues following a bee sting—Africanized or not—could well increase the consequent morbidity by way of added cardiovascular stress, associated traffic accidents, or irrational behavior such as attempting to destroy beehives without adequate personal protection or experience.

Bee-Sting Treatment and Prevention

Because Africanized bee-sting incidents tend to involve hundreds or thousands of bees recruited in the attack, the first response of a victim should be to escape. Most healthy children and adults can outrun a swarm of bees long enough to find shelter or to reach a relatively safe distance from the hive. The very young and old, physically disabled, and persons with cardiopulmonary disease, however, may not be able to reach a safe distance before collapsing.

Treatment principles of major sting reactions are essentially the same (Table 2), whether the offending bees are of European or African descent; these have been reviewed elsewhere.[34,47,55,67] Patients who have had hypersensitivity reactions, multiple stings, or single stings in the mouth or neck should receive immediate medical attention and close observation. Most people who die of bee-sting hypersensitivity reactions are those who do not receive medical attention within the first hour.[51]

When available, the offending bee should be submitted for precise identification. Victims of insect bites and stings notoriously incriminate the wrong insect.[68] Proper identification becomes paramount when considering immunotherapy or when investigating the possible arrival of Africanized bees into a new region.

Prevention and Education

The best approach to Africanized honeybee stings is prevention. Because sting incidents generally occur near a hive, avoidance is key. Children must be taught not to play with or near hives. Untrained persons should not attempt to move or destroy beehives on their own. Instead, the discovery of a wild hive should be reported to the appropriate authorities.

Hypersensitive persons have long been counseled to reduce their chances of being stung by avoiding the use of perfumes or hairsprays and not wearing brightly colored clothes. Food and garbage may occasionally attract honeybees, so care should be taken to conceal these items. When outdoors, shoes, long pants, and long sleeves should be worn. In high-risk bee-sting areas (such as areas with established Africanized honeybee colonies), nonallergic persons should also follow these guidelines. Occupations most associated with honeybee stings are those with extensive outdoor exposure: landscapers, park rangers, utility workers, and construction

TABLE 2.—*Emergency Treatment of Honeybee Stings*

Reaction Type	*Treatment*
Local reactions	Remove remaining stingers Wash open wounds Cold compresses; elevate extremity Anesthetics/analgesics—topical, enteral
Major local reactions*	Antihistamines Close observation Epinephrine, if cardiopulmonary compromise is suspected Oral corticosteroids
Systemic reactions*	Epinephrine Antihistamines Aminophylline Parenteral corticosteroids Cardiovascular monitoring and support, including intravenous fluids, vasopressors, dialysis Airway protection

*In addition to treatment measures given for local reactions.

personnel.[34] Bees are sensitive to vibrations, and many attacks have occurred after lawn mowers or tractors have gotten too close to a hive.

Successful honeybee-management programs in South and Central America have targeted three public health priorities: widespread education, readily accessible first aid (which has occasionally included the distribution of emergency bee-sting kits), and the creation of honeybee-control squads to remove or destroy troublesome hives.[5] Honeybee-control programs in Venezuela decreased the annual number of deaths in that country from almost 100 in 1978 to only 20 in 1985.[30]

Learning from our southern neighbors, communities in Texas are successfully instituting public awareness campaigns and are developing emergency protocols for responding to bee-sting incidents.[1] Reports of major stinging attacks trigger an immediate and integrated response by fire and emergency medical departments. Citizens are being informed about Africanized honeybees and about bee stings through public service announcements, mailings, and school projects.

Immunotherapy

Bee-sting immunoprophylaxis can be useful in many circumstances, and much has been written elsewhere about the appropriate patient selection, performance, efficacy, and shortcomings of immunotherapy.[55,69-75] Because the composition of Africanized honeybee venom is essentially the same as that of European honeybee venom, patients having hypersensitivity reactions to Africanized honeybee stings should be skin tested or provided immunoprophylaxis according to the same guidelines. Any person displaying bee-sting anaphylaxis should be referred to an allergist who can then determine whether or not that person would benefit from immunotherapy. The decision to initiate immunoprophylaxis for Africanized honeybee stings must be individualized because the clinical manifestations resulting from multiple Africanized honeybee stings are often the result of venom toxicity rather than allergy, and the benefit of immunoprophylaxis under these circumstances is therefore questionable. The efficacy of immunoprophylaxis with derivatives of European honeybee venom in preventing hypersensitivity reactions to Africanized honeybee stings may be equivalent; however, this has not yet been demonstrated.

Looking Toward the Future

As we look ahead to the Africanization of honeybees in North America, our anxiety should be tempered with the knowledge that African societies have lived peacefully with the African honeybee for thousands of years while managing its hives and harvesting its honey.

As more North American honeybee colonies become Africanized, it is probable that major bee-sting incidents will occur with increasing frequency. We will be facing the following public health problems:

- Getting emergency medical care to bee-sting victims quickly enough so that life-saving treatment can be instituted; and
- Preventing citizens from doing themselves more harm as a result of ignorance, misunderstanding, or overreacting to the Africanized honeybees.

The solutions to these problems will require integrated, well-prepared emergency medical services and public education. Health care professionals can help decrease the threat of this Africanized honeybee by being well informed, providing factual information to their patients, and participating in local and regional policy development before the bees arrive.

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Poisonous Snakebite in Utah

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A retrospective study was done of poisonous snakebite in Utah to determine the current epidemiology and scope of treatment, reviewing emergency department logs and other sources statewide for a 69-month period. Of 61 cases of poisonous snakebite identified, 13 occurred in snake hobbyists or venom laboratory personnel and were considered nonaccidental, and 48 were inflicted by native noncaptive snakes. These bites were considered accidental, and all were presumed to be from rattlesnakes. Nearly three fourths of the victims were male, ranging in age from 2 to 56 years (mean, 22 years). Most accidental bites occurred in areas of high human populations, during the summer months, in the afternoon or evening hours, and during recreational activities. Of the 48 bites, 11 (23%) were provoked. Two thirds of bites were on the upper extremities, and a third were on the lower extremities. More than half of the victims had no first-aid treatment recorded. Of those who did receive first aid, many were subjected to possibly harmful treatments, including tourniquets and ice application. The median time to a hospital was 68 minutes, with a range of 15 to 440 minutes. Swelling and discoloration were the most common signs and pain and paresthesia the most common symptoms. Half the bites resulted in minimal or no envenomation, 17 (35%) produced moderate envenomation, and 6 (12%) severe envenomation. Most patients with moderate or severe envenomation received antivenin, but the dosages given were usually less than recommended dosages. Five patients received surgical treatment based on clinical findings. One child died in a snake-handling incident. Long-term morbidity was unknown due to lack of follow-up. The Utah Poison Control Center was poorly utilized as a reporting and informational resource.

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Poisonous snakebite is an uncommon emergency in the United States, even in states with large populations of indigenous poisonous snakes.[1] Despite many reports of different successful treatments, guidelines for the general management of poisonous snakebite in this country are not universally accepted.[2-6] In Utah, 20 poisonous snakebites were estimated to occur annually, based on a 1959 survey.[1] Despite this limited opportunity for clinical experience, various practitioners in the state have advocated a wide variety of first-aid measures and hospital treatments. To better define the epidemiology of poisonous snakebite in Utah and to examine the scope of prehospital and hospital care provided for these injuries, we did a retrospective study of snakebite in the state over a five-year period.

Cases and Methods

The emergency department logs of all Utah hospitals identified by the Utah Hospital Association as having 20 beds or more (21 total) were examined by diagnosis for the period January 1985 through September 1989. The hospital records of all patients with a diagnosis of poisonous snakebite or related diagnoses—snake venom poisoning or envenomation—were reviewed. In addition, names of snakebite victims were obtained from the Venom Research Laboratory at the Veterans Affairs Medical Center and the Utah Poison Control Center (UPCC) in Salt Lake City. Data were obtained pertaining to geographic location, type of snake, time of bite, victim activity, bite location, first aid, signs and symptoms, laboratory values, hospital treatment, complications, and outcome. The severity of envenomation was graded as none, mild, moderate, or severe based on presenting signs, symptoms, and laboratory values using the method described by Wingart and Wainschel (Figure 1).[7] The prevalence of bites was calculated using a mean population of 1,675,000 for the state over the study period (source: State of Utah, Population Estimates Committee). Linear regression was performed when appropriate, with $r > .8$ considered a good correlation.

Results

We identified 66 cases of poisonous snakebite or envenomation. Of these, 54 were found through the

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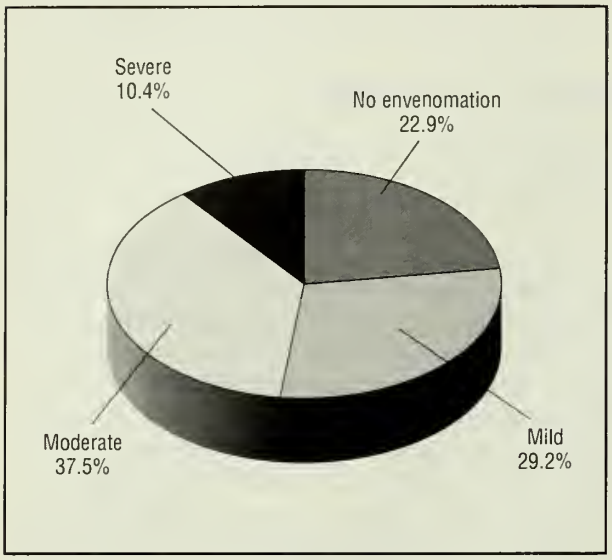

Figure 1.—The grade of envenomation on initial presentation in 48 patients bitten by native noncaptive snakes is shown. The initial grading system is based on the method described by Wingert and Wainschel[7]: No envenomation (11 patients) = no local or systemic reactions; mild (14 patients) = local swelling but no systemic reactions; moderate (18 patients) = swelling that progresses beyond the site of the bite, together with a systemic reaction or laboratory changes such as a fall in hematocrit; severe (5 patients) = pronounced local reaction, severe symptoms, and laboratory changes.

emergency department log review, and 8 were reported by the Venom Research Laboratory. Although 269 snakebite calls were handled by the UPCC during the study period, only 55 were thought to involve poisonous snakes, many were from adjacent states, and few resulted in hospital evaluation. Of 54 cases treated in Utah hospitals, only 9 had been reported to the UPCC.

Of the 66 confirmed cases, 5 were eliminated: 4 occurred in other states but were treated in Utah, and 1 person was not bitten but was squirted in the eye with venom while skinning a dead rattlesnake. This left 61 cases of poisonous snakebite occurring in Utah over the study period, for an overall incidence of 12.8 bites per year, or about 0.8 bites per 100,000 per year.

Of the 61 bites, 13 occurred when human-snake contact was planned. These bites were considered nonaccidental.

In nine cases, laboratory personnel were bitten at two different venom laboratories. Four of these laboratory bites were by exotic species, and five were by rattlesnakes indigenous to the United States, but not to Utah. One of these persons was bitten on five separate occasions and another twice. One bite by a cobra with ligated venom ducts showed no signs of envenomation. The other exotic bites showed signs of moderate to severe envenomation, but the grading scale described is specific only for pit-viper envenomation. The four rattlesnake bites resulted in mild to moderate envenomation. In only three instances did professionals seek medical treatment, despite signs of envenomation in eight bites. The bite by the "venomless" cobra required only tetanus immunization. A bite by one exotic snake resulted in a severe case of coagulopathy that was treated only with supportive care because specific antivenin was not available in this country. A mild case of rattlesnake envenomation was treated with antivenin, complicated by a mild allergic reaction. There were no deaths from snakebite in laboratory personnel.

Snake hobbyists accounted for four nonaccidental bites. All were by rattlesnakes, species unknown. One hobbyist was bitten while force-feeding a pet snake, two others while playing with pet snakes, and one child died after being bitten by a pet rattlesnake placed on her by a hobbyist. Two bites showed mild envenomation, one moderate, and one severe. This last case was the only death encountered during the study period.

The remaining 48 cases represent bites by native noncaptive snakes. These bites may be considered accidental because contact between humans and snakes in these incidents was not planned. We think that the data obtained from such accidental bites more truly reflect the epidemiology of snakebite by indigenous species occurring in their natural environment. The rest of the results will refer to these 48 patients unless otherwise noted.

The incidence of native, noncaptive poisonous snakebite was 11 bites per year (0.7 bites per 100,000 per year). Of the 48 bites, 45 were thought to be inflicted by rattlesnakes. Although species differentiation was not possible using information in hospital records, the geographic location of the bites suggests that the Great Basin rattlesnake (*Crotalus viridis lutosus*) was the culprit in about 90% of cases. The other three bites showed smaller or indistinct fang marks but no signs of envenomation. These bites may have been inflicted by other snakes, but were treated as rattlesnake bites based on the patients' histories.

Of the 48 victims, 35 (73%) were male. The ages of the victims ranged from 2 to 56 with a mean of 22 ± 10.9 years. There was no bimodal age distribution.

All but five of the bites occurred along the front range of the Wasatch Mountains, which corresponds with the highest human populations. Half of the snakebites occurred during the months of June and July, with all occurring between March and October. More than half the bites occurred between 5 PM and 10 PM, with nearly all bites occurring between 12 noon and 10 PM. In all, 16 victims (33%) were bitten on a lower extremity, 31 (65%) on an upper extremity, and 1 was bitten on the trunk. Most snakebites occurred during recreational activities such as hiking, horseback riding, climbing, camping, fishing, and motorcycle riding. In 10 cases (23%), the victim admitted to handling or otherwise provoking the snake. Victims' use of alcohol was not reliably documented.

Nearly two thirds of victims (63%) had no first-aid treatment documented. In those cases in which first-aid measures were reported, 12 (25%) had tourniquets or

TABLE 1.—*Frequency of Occurrence of Symptoms and Signs in 48 Snakebite Victims*

Presentotion	*Frequency, No. (%)*
Symptoms	
Pain	39 (81)
Paresthesia	23 (48)
Nausea and vomiting	15 (31)
Hyperesthesia	7 (15)
Weakness, "dizziness"	5 (10)
Taste changes	3 (6)
Signs	
Fang marks	48 (100)
Swelling	40 (83)
Discoloration	33 (69)
Bleeding	14 (29)
Bullae	7 (15)
Fasciculations	4 (8)
Tissue necrosis	3 (6)
Hypotension	2 (4)
Rigors and diaphoresis	1 (2)
Petechiae	1 (2)

ace bandages applied, 8 (17%) had ice applied to the wound, 3 (6%) had an incision, 6 (13%) had suction, 2 (4%) received elevation, and 1 (2%) had cleansing. The median time taken from the time of the bite to reach a hospital was 68 minutes, with a range of 15 to 440 minutes.

The frequency of reported signs and symptoms is shown in Table 1. Fang marks, swelling, and discoloration or ecchymosis were the signs present in most of the patients, and pain and paresthesias were the most common symptoms.

More than half (52%) the bites resulted in minimal or no envenomation, whereas 18 (38%) had moderate and 5 (10%) had severe envenomation (Figure 1). A variety of laboratory tests were done for 33 patients (Table 2). Although patients with moderate to severe envenomation were more likely to have abnormal laboratory results ($P < .05$), this observation is moot because laboratory values were used in determining envenomation severity.

Table 3 shows the incidence of antivenin administration and surgical treatment. Of the 48 patients, 27 (56%) received antivenin, although the number of vials received varied greatly (range, 1 to 15; mean ± standard deviation, 3.0 ± 3.8). Indications for antivenin administration or choice of number of vials given was not documented. There was no correlation between the severity of envenomation and the number of vials of antivenin administered ($r = .56$). An acute allergic reaction developed in one patient (whose horse serum skin test was negative), treated successfully with corticosteroids. A case of serum sickness was reported in a patient who received nine vials of antivenin for a moderate envenomation. His symptoms resolved after 12 days with corticosteroid treatment.

Two patients with severe and three with moderate envenomation received surgical treatment. Surgical treatment ranged from incision of the bite site to wound excision with fasciotomies and antibiotic perfusion catheters. Indications for any surgical approach were based on clinical findings. Compartment pressures were measured in only one of three patients undergoing fasciotomy.

Other supportive treatments given in the emergency department or hospital included antibiotics, immobilization of the extremity at the heart level, ice, antihistamines, analgesics, steroids, tetanus immunization, constricting bands, and wound cleansing with or without debridement.

Long-term morbidity was not documented in the medical records of any of the 48 victims of native, noncaptive poisonous snakebite. We did not have access to clinic or office records of physicians who might have provided subsequent care. There were no fatalities in this group.

Discussion

Notification of poisonous snakebite in Utah is not required, and the true incidence is not known. This review is based on cases of patients who sought medical care for snakebite at Utah hospitals. Those who consulted a private physician or small hospital or clinic or who did not seek care are not represented, with the exception of a few laboratory personnel. Despite this limitation, the calculated incidences of 12.8 per year for all poisonous snakebites in Utah and 11 per year for poisonous bites by native, noncaptive snakes are probably as accu-

TABLE 2.—*Laboratory Results in 33 Snakebite Victims*

Loborotory Test	*Normol Volues*	*Meon ± SD*	*Potients With Abnormal Volues ond Moderote or Severe Envenomotion, No.**	*(%)*
Platelet count, × 10⁹/liter	140-440	227.2 ± 95.3	6/33	(18)
Prothrombin time, seconds	13.5-17.0	15.1 ± 5.9	3/26	(12)
Partial thromboplastin time, seconds	25-36	67.3 ± 98.9	13/27	(48)
Fibrinogen, grams/liter†	1.5-3.5	1.74 ± 0.08	4/17	(17)
Fibrin degradation products, µg/ml	0-5	52.3 ± 106.3	6/11	(54)

SD = standard deviation

* Not every patient had every laboratory test.
†To convert to conventional units (mg/dl), multiply by 100.

TABLE 3.—*Treatment in 48 Snakebite Victims*

Surgery (5 potients)				*Antivenin Administrotion (37 potients)**			
	Envenamatian	*Type of*	*Indicatians*		*Envenomation*	*No. af Vials*	
Patients, No.	*Grade*	*Procedure*	*Given*	*Potients, No.*	*Grode*	*Range*	*Mean ± SD*
1	Moderate	Finger "fasciotomy" skin graft	No capillary refill	14	Minimal	0-5	1.4 ± 1.8
1	Moderate	Wound incision	"To allow drainage"	17	Moderate	0-15	5.4 ± 4.6
1	Severe	Volar and dorsal hand fasciotomies, carpal tunnel fasciotomy	"Black" hand with decreased sensation and capillary refill	6	Severe	2-9	5.0 ± 2.4
2	Severe	Wound excision, hand fasciotomies, perfusion catheters	Elevated compartment pressures >15 mm of mercury (1 patient); clinical findings of decreased capillary refill and pulses, contracture	37	All	0-15	3.0 ± 3.8

SD = standard deviation

*r = .56.

rate as can be practically obtained. This is considerably less than the incidence of 20 poisonous bites per year in Utah previously reported.[1] The previous estimate, however, was based on a 1958-1959 survey of selected physicians and hospitals and was extrapolated from 20 bites reported over a two-year period.

Poison control centers would seem an ideal resource for tracking poisonous snakebite data. Although many snakebite calls were received during the study period by the UPCC, only a few could be confirmed by hospital records. Some of these patients may have been treated in other states or by private physicians or clinics. Some may have decided not to seek medical care, for unknown reasons.

Conversely, most of the cases found in emergency department logs had not been reported to the UPCC, indicating a reluctance of Utah physicians to use this valuable resource. Other states have instituted snakebite registries on local or statewide levels, but reporting remains voluntary.[6] Even a well-utilized reporting system may not reflect the actual incidence of poisonous snakebite, as some bites result in little or no envenomation, and medical care may not be sought.

The descriptive statistics regarding victims' age, sex, activity, month, time of day, and anatomic site of bites do not differ greatly from those reported for rattlesnake bites in other series.[2,4,8] Young men and children engaged in outdoor recreational activities during summer afternoon and evening hours have been reported to be the most likely to be bitten. All but one of our victims was bitten on an extremity, the most commonly reported bite site, but there was no predilection for lower extremity bites in children, as reported by others.[2] Bites were preventable in at least 11 of our cases (23%) when victims admitted to handling or provoking the snake. In another report, bites were preventable in more than half of 282 cases.[4] We were unable to document alcohol use in our retrospective study, but others have noted intoxication in 16% to 28% of patients.[4,8]

Likewise, the use of first-aid measures in the field appears similar to that reported elsewhere. Most of our patients had no first aid documented, whereas in a previous report, various first-aid treatments were given in two thirds of 282 patients.[4] Many treatments that have been discouraged, such as tourniquets, ice, and incision and suction, continue to be used in Utah and other states.[4] Considerable morbidity of many of these well-intentioned measures has been documented.[6] There remains a lack of scientific evidence for the efficacy of measures such as suction and constrictive bands. Suction has been shown to remove a portion of injected venom in animal models only if applied within five minutes of the time of the bite.[9] Likewise, it has been shown in a swine model that a constricting band limited venom absorption without increasing swelling.[10] Neither of these findings has been confirmed in humans. Those measures which seem to have some validity are avoiding excessive activity, immobilizing the bitten extremity, and transporting the victim to the nearest hospital.[4,6]

Hospital treatment of poisonous snakebite remains even more controversial than first-aid measures. No universally accepted approach exists for the use of antivenin, surgical treatments, or other modalities. Even a uniform system of grading envenomation severity is not agreed on.

A review of current reference materials available to clinicians and poison control centers shows a wide variation in indications for and amount of antivenin to be used.[6,11,12] Some authors have called for controlled studies to verify the efficacy of antivenin, but these have not as yet been done. One group chose to treat poisonous snakebite without antivenin and reported good results in ten cases of rattlesnake envenomation.[3] Most authors, however, insist that antivenin is the mainstay of the treatment of serious envenomation.[6,11,12] Russell has recommended administering from 5 vials of antivenin for minimal envenomation to 20 or more in severe cases.[6]

Others recommend withholding antivenin for all but moderate to severe envenomation, with doses ranging from 0 to more than 20 vials, depending on the clinical presentation.[4,12] It is not surprising, therefore, to note that there was no consistency in the amounts of antivenin used in our series of patients. Amounts used were generally less than those recommended by the manufacturer and by most authors.[11-13] We were unable to determine if any increased morbidity was associated with the failure to use recommended doses of antivenin in our small series. It is likely that consultation with a regional poison control center would have resulted in a more consistent use of antivenin.

Generally, most authors who advocate the use of antivenin in cases of poisonous snakebite recommend no antivenin for bites with fang marks only and no signs or symptoms of envenomation. Observation for as long as eight hours has been recommended for these patients to ensure that late-developing signs are not missed. For patients with mild envenomation, various authors recommend giving 0 to 8 vials as an initial dose. For moderate envenomation, 0 to 10 vials have been recommended, and for severe envenomation, 5 to 20 vials or more. Even greater doses of antivenin have been recommended in children and in those who do not respond to the initial dose with decreased progression of swelling in the first hour of antivenin treatment. All authors who use antivenin recommend skin testing before administering antivenin, but warn that allergic reactions may still be seen in those with negative skin tests, as was noted in the one patient in our series with an allergic reaction to antivenin. Prophylactic antihistamine administration has been recommended by some.

Likewise, indications for and type of surgical therapy are seldom agreed on. Some authors take a strong stand against any surgical intervention for poisonous snakebite, regardless of tissue pressures.[6] Others advocate excision of the bite site and early fasciotomy based on clinical indicators.[14,15] Many have taken a conservative approach, advocating the use of antivenin, with fasciotomy being done only if indicated by clinical signs and elevated tissue pressure measurements.[2] Unfortunately, none of these approaches is supported by controlled clinical studies. In our series, only five patients received surgical interventions, and long-term outcomes were not available, so we can make no conclusions.

Finally, the use of various supportive measures has been addressed by several authors. Many have recommended the prophylactic use of antibiotics, even though the incidences of infection in their series are low.[2,7,8] Steroids and antihistamines are of no value in envenomation, but their use is indicated for allergic complications when these occur.[6] Certainly, the application of ice has no place in the treatment of envenomation, and its use has been shown to result in gangrene in some cases.[6] Supportive measures were recorded infrequently in our series, with antibiotics, immobilization, and ice being those most often applied. No detrimental effects of ice application were recorded, but follow-up was not available.

The UPCC was an underutilized resource for snakebite reporting and treatment recommendations. We encourage Utah physicians to report all snakebites to the UPCC for continued epidemiologic study and assistance with current management guidelines. It is likely that a more consistent use of antivenin would have resulted from routine consultation with the UPCC on all snakebite cases. Although too few cases were treated surgically in our series to allow specific inferences, we support the approach that surgical intervention be based on clinical findings confirmed by elevated tissue compartment pressure measurements. Routine consultation with a poison control center is recommended for epidemiologic reporting of snakebite and consistency of antivenin treatment.

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Conferences and Reviews

Syphilis
A Tale of Twisted Treponemes

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Based on a discussion presented at Medical Grand Rounds in the University of California, San Francisco, School of Medicine, this article has been edited by Nathan M. Bass, MD, PhD, Associate Professor, Department of Medicine.

Despite the widespread availability of effective treatment, the incidence of primary and secondary syphilis in the United States is on the rise. In addition, syphilis is occurring in a substantial number of patients infected with the human immunodeficiency virus (HIV), thus adding to the complexities of diagnosis and treatment. Primary syphilis represents a disseminated infection, often accompanied by abnormalities of the cerebrospinal fluid, that may pass unrecognized and progress to the myriad manifestations of secondary syphilis. The diagnosis of syphilis in patients with mucosal or skin lesions may be made by darkfield examination; once lesions have resolved, serologic tests are required. Patients with latent syphilis may have asymptomatic neurosyphilis and risk progression to tertiary disease. The diagnosis of asymptomatic neurosyphilis is necessary to determine the optimal treatment of patients with latent disease. The diagnosis of active neurosyphilis generally requires an inflammatory cerebrospinal fluid profile and a reactive cerebrospinal fluid VDRL test. Syphilis is common in HIV-infected patients, who may have an altered antibody response to infection and an apparent increased incidence of neurologic complications. The preferred treatment at all stages is penicillin, which is also the only recommended therapy for neurosyphilis. The optimal treatment of syphilis in HIV-infected patients is unknown.

(Flores JL: Syphilis—A tale of twisted treponemes. West J Med 1995; 163:552-559)

Why should we be concerned today about syphilis, a disease that is readily cured by a widely available, inexpensive medication? After an initial precipitous decline in the number of cases after the development of penicillin, there has been an overall slow but sustained increase in the incidence of primary and secondary syphilis in the United States, which has only recently begun to decline (Figure 1).[1] In the 1970s and early 1980s, this increase occurred predominantly in the male homosexual community; with behavioral changes after the recognition of human immunodeficiency virus (HIV) transmission, rates have declined in this group.[2] More recently, the incidence of syphilis in heterosexual men and women has increased rapidly; concomitantly, the incidence of congenital syphilis has risen substantially over the past ten years.

Syphilis, therefore, is on the rise. This increase, and the added complexities of diagnosing and treating syphilis in the rising number of HIV-infected patients, makes review of this topic particularly timely.*

*See also the editorial by S. A. Lukehart, PhD, "Modern Syphilis—Still a Shadow on the Land," on pages 587-588 of this issue.

Early Syphilis

Syphilis is usually, but not exclusively, transmitted by sexual contact. Three to four weeks after exposure, 50% to 60% of patients will have a chancre at the site of inoculation (primary syphilis).[3] This characteristic ulcerative lesion is usually solitary and painless, with a clean, indurated base. Before any lesion appears, however, the causative agent, *Treponema pallidum*, is already widely disseminated. In fact, by the time primary syphilis is diagnosed, almost 25% of patients may have cerebrospinal fluid (CSF) abnormalities attributable to the infection.[4]

Because chancres are typically painless and heal in three to six weeks without treatment, primary syphilis infection may pass unnoticed. Virtually all untreated patients progress to secondary syphilis within four to ten weeks of the initial exposure. This stage is famous for its vast array of manifestations; symptoms commonly include fever, generalized lymphadenopathy, and a diffuse rash that typically involves the palms and soles. Mucosal lesions of secondary syphilis include condylomata lata, papular lesions in intertriginous areas covered by a grayish exudate teeming with treponemes,

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control and Prevention
CNS = central nervous system
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption [test]
HIV = human immunodeficiency virus
RPR = rapid plasma reagin [test]

and equally infectious mucous patches. Cerebrospinal fluid abnormalities are not uncommon, even in neurologically asymptomatic patients; *T pallidum* has been isolated from CSF in 30% of patients with primary or secondary syphilis.[5] Early symptomatic neurosyphilis—aseptic meningitis, cranial nerve palsies, eye manifestations—is also well known to occur in patients with secondary syphilis.[6]

Should the disease escape detection and treatment during this phase, all these manifestations, including central nervous system (CNS) involvement, will generally follow an initially benign course.[7] Patients will pass into "early latency," defined as the period of time during the first year of infection after all manifestations other than serologic markers have resolved. During this year, untreated patients are at risk for relapse: secondary syphilis will recur in about 25%.[8] Patients in this stage are, therefore, still potentially infectious. Primary, secondary, and early latent stages of infection are referred to together as early or infectious syphilis.

Diagnosing Early Syphilis

Darkfield examination is useful for making the diagnosis of syphilis in a patient with a chancre or mucosal lesion. *Treponema pallidum* is identified by its characteristic "corkscrew" structure and motility. This technique should not be used for oral lesions because the presence of nonpathogenic treponemes may result in a false-positive test. Although it has not been studied recently, the darkfield examination is widely regarded as both sensitive (95% in 1 series of seronegative patients with primary syphilis)[9(pp516-518)] and specific; however, the usefulness of the test depends on the experience of the observer and adequacy of the specimen. Also, the use of antibiotics topically or parenterally may result in a false-negative test. For these reasons, a darkfield examination should not be reported as negative until it has been repeated two or three times, especially in a patient with a suspicious lesion.

Patients with latent disease by definition have no cutaneous or mucosal lesions. Diagnosis rests on serologic tests, as shown in Figure 2. In all of these, antigen is provided to bind with antibody produced in response to syphilitic infection. Various mechanisms are then used to detect the formation of antigen-antibody complexes, such as flocculation in the VDRL and rapid plasma reagin (RPR) tests, fluorescence in the fluorescent treponemal antibody-absorption (FTA-ABS) test, or hemagglutination in the microhemagglutination-*T pallidum* test.

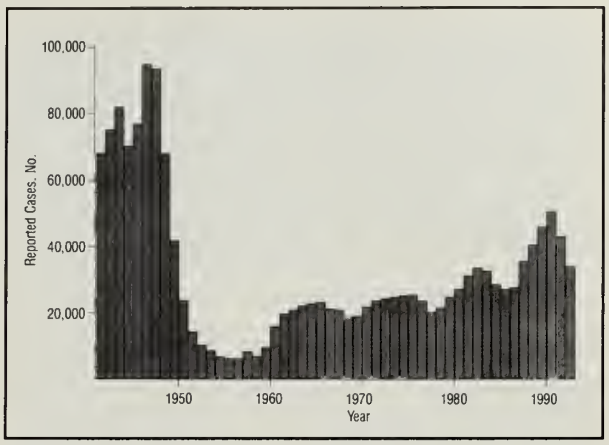

Figure 1.—The graph shows the number of cases of primary and secondary syphilis in the United States from 1941 through 1992.

Antibodies generated in response to syphilis fall into two broad categories. The first are the "reaginic" or nontreponemal antibodies. These antibodies, which react with cardiolipin, also reflect evidence of treponemal infection, an adventitious discovery that formed the basis of the Wassermann test, as well as the currently used VDRL and RPR tests. Titers of these antibodies generally reflect disease activity and are used to monitor response to treatment. Whereas either the VDRL or the RPR test may be assessed serially to monitor response, the titers of these two tests are not interchangeable; therefore, the same test should be used throughout follow-up.

Treponemal tests are conceptually simple: they are antibodies directed against *T pallidum* antigens. Most commonly used are the FTA-ABS and the microhemagglutination-*T pallidum* tests. The major use of these tests is to confirm positive nontreponemal tests because treponemal tests are positive in the vast majority of infected patients, whatever the stage.

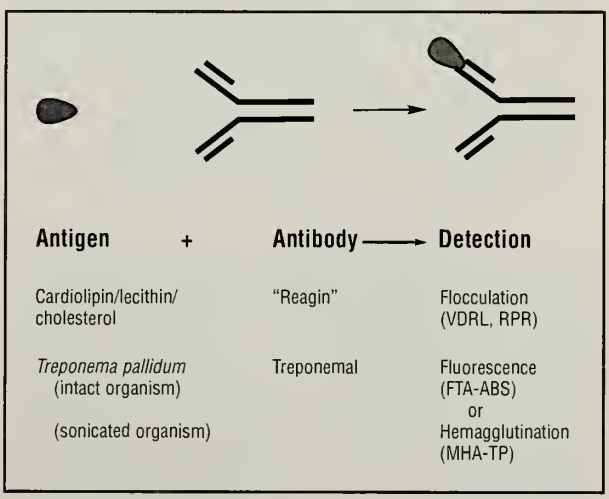

Figure 2.—Serologic tests for syphilis are shown. FTA-ABS = fluorescent treponemal antibody absorption, MHA-TP = microhemagglutination-*Treponema pallidum*, RPR = rapid plasma reagin

TABLE 1.—*Sensitivity of Serologic Tests for Syphilis**

Test	Stage of Infection		
	Primary, %	Secondary, %	Tertiary, %
VDRL	62-75	99	70
FTA-ABS	81-100	100	100

FTA-ABS = fluorescent treponemal antibody-absorption

*From Hart.[10]

Nontreponemal tests may be unreactive initially in 30% to 40% of cases of primary syphilis compared with a darkfield gold standard; therefore, a negative test should not be used to rule out the disease (Table 1).[10,11] The treponemal antibody has a higher sensitivity in primary syphilis.[10] By the time of secondary syphilis, virtually all patients produce both treponemal and nontreponemal antibodies. In an untreated patient, the nontreponemal antibody response can diminish over time, but the treponemal antibody response should remain positive essentially lifelong.

Assessing the specificity of these serologic tests is problematic: the difficulty, of course, is in finding a population with a near-zero probability of syphilis to ensure that a positive test is actually false-positive. An innovative study tested 250 nuns with a stated history of no infectious or congenital syphilis; in some cases the nuns' mothers were interviewed for completeness.[12] In this group, the VDRL test was 100% specific, whereas the FTA-ABS test had a 1.2% false-positive rate. The three false-positive tests included one in a person with active pulmonary tuberculosis and another in a person with a history of rheumatoid arthritis. In another study, better than 99% specificity was found for the VDRL and FTA-ABS tests in more than 1,000 healthy volunteers, but substantially lower specificity was reported for both tests in hospitalized patients with no known history of syphilis.[13] These data are difficult to interpret without more information to assess the likelihood of a past syphilis infection and the incidence of known causes of biologic false-positive tests in both groups. The cautionary message is that in an acutely or chronically ill patient, the specificity of serologic tests may not be as high as in healthy patients.

TABLE 2.—*Treatment of Primary and Secondary Syphilis*

Therapy	Regimen
Recommended	
Benzathine penicillin G	2.4 million units IM in 1 dose
For penicillin-allergic patients	
Doxycycline	100 mg orally 2 ×/day for 2 wk, or
Tetracycline	500 mg orally 4 ×/day for 2 wk
Third-line therapy	
Erythromycin	500 mg orally 4 ×/day for 2 wk

IM = intramuscularly

Treatment of Early Syphilis

Treatment is the same for all phases of early disease—primary, secondary, and early latency (Table 2). The treatment of choice is the administration of benzathine penicillin G, 2.4 million units intramuscularly, shown to be at least 95% effective in large studies.[14,15] Whereas the use of benzathine penicillin is highly effective, it achieves negligible CSF levels.[16] Remember that a substantial number of patients with early syphilis have asymptomatic CSF involvement; the vast majority, however, are able to resolve early infection with treatment that does not provide treponemicidal CSF levels. The clearance of the CSF does appear to require an intact immune response even with appropriate antibiotics.[17]

For penicillin-allergic patients, doxycycline is the best alternative therapy; erythromycin has less than 90% efficacy.[14] Ceftriaxone sodium achieves excellent CSF penetration, but data are too limited to recommend it as an effective alternative therapy.

Treatment response is gauged by a fall in nontreponemal antibody titers, because early clinical manifestations resolve without treatment. According to previous guidelines, patients treated for early syphilis should show a nontreponemal antibody titer decline of at least fourfold (2 tubes) at three months and eightfold (3 tubes) at six months.[18] A slower or smaller decline in the titer has been considered worrisome for possible treatment failure. A fourfold rise in antibody titer or a return of clinical manifestations indicates treatment failure or reinfection.

A recent study from Canada has revised these general guidelines. In more than 1,000 patients treated for early syphilis and observed for as long as three years, the observed rate of nontreponemal antibody titer decline was much slower than previously expected.[19] In fact, many patients considered cured in this study by their eventual titer decline would be considered treatment failures by the previous criteria. Patients with early latent syphilis had a slower and smaller drop in titer (fourfold decrease at 12 months) than patients with primary and secondary syphilis (fourfold decrease at 6 months and eightfold decrease at 12 months). Given these results, at least a fourfold antibody titer decline within 6 months for primary and secondary syphilis and within 12 months for early latent syphilis can be considered evidence of a treatment response. A return to negative serologic tests ("seroreversion") is too stringent a test for cure because only 63% of the treated study patients seroreverted in three years. In addition, despite previous teaching that treponemal antibodies persist even after adequate treatment, in this study about 25% of treated patients became treponemal antibody-negative over the three-year period. Of note, all patients who seroreverted in this study had a first episode of infection, and most had primary syphilis.

Latent Syphilis and Asymptomatic Neurosyphilis

From such studies as the infamous Tuskegee study and a large study in Oslo,[8] we know that undetected or

inadequately treated syphilis will progress to "late latency," a phase of disease occurring at least a year after infection and detectable only by serologic tests. Most untreated patients will persist in latency for life, although some will lose serologic markers. About a third, however, go on to manifest tertiary disease, which can take a variety of forms: neurologic, including general paresis and tabes dorsalis; cardiovascular, with aortitis, aortic regurgitation, and aortic aneurysm; and gummatous, characterized by granulomatous-like lesions infiltrating the skin, soft tissues, bone, liver, or any organ in the body.

All patients with latent or tertiary syphilis require treatment. Our goal in treating patients with latent disease is to identify those who need more intensive treatment for asymptomatic neurosyphilis. The usual clinical question is, "Does my asymptomatic patient with positive syphilis serologies really need a lumbar puncture to rule out asymptomatic neurosyphilis, or can he or she be simply treated presumptively for latent disease?" In attempting to answer this question, we will start by considering the prevalence of asymptomatic neurosyphilis in patients with late latent infection.

Historical data from large series suggest that 5% to 10% of patients with late latent syphilis may have asymptomatic neurosyphilis.[20(pp72-73)] Two studies have found 0% prevalence in a small number of patients.[21,22] A study of CSF abnormalities in patients with syphilis, however, found that 3 of 15 patients (20%) with late latent syphilis had a positive CSF-VDRL test.[5] Taking all of these studies into account, we may infer that the prevalence of asymptomatic neurosyphilis is likely low, but not negligible. The prevalence in HIV-infected patients, however, appears to be substantially higher, as I will discuss.

Do any other factors predict a risk of asymptomatic neurosyphilis? Age, or more precisely, the duration of infection, may be helpful. In the long-term natural history study from Oslo, none of 169 patients with latent syphilis for more than 30 years had asymptomatic neurosyphilis. Presumably, neurologic involvement eventually becomes symptomatic, so that after 30 years no patient is left with asymptomatic neurologic involvement. We cannot assume, however, that because a patient is elderly, the infection must have been acquired many years ago. A recent study from Hartford described the cases of 35 patients older than 60 with early syphilis[23]; consistently, 2.5% to 3% of cases of primary and secondary syphilis in the US are diagnosed in patients older than 55 years.[1]

In addition, CSF abnormalities in early syphilis have long been recognized as prerequisite for the development of neurosyphilis in untreated patients.[6] Patients with normal CSF during the first two years of infection have a negligible risk of having symptomatic neurologic involvement in late disease.[6]

A decision-analysis model compared the strategies of lumbar puncture in patients with asymptomatic late syphilis to diagnose and treat neurosyphilis versus simply treating patients for presumed uncomplicated latent disease.[24] Outcome estimates for cure using the two strategies slightly favored the one using lumbar puncture (99.75% versus 99.95%); however, the rate of complications in the group having lumbar puncture (0.3%) was estimated to exceed the marginal benefit.

TABLE 3.—*Criteria for Cerebrospinal Fluid Examination in Latent Syphilis*

Neurologic or ophthalmic signs or symptoms
Evidence of tertiary syphilis—aortitis, gummas
Failure of treatment of early syphilis
Nonpenicillin therapy planned
Serum nontreponemal antibody titer >1:16 (unless duration of infection is <1 yr)
Human immunodeficiency virus infection

If, as this analysis suggests, it is not necessary to subject indiscriminately all asymptomatic patients with latent syphilis to lumbar puncture, who then should be screened (Table 3)? Any patient with untreated syphilis for less than 30 years but longer than a year should be considered for screening. Infection for less than a year, even with asymptomatic CSF abnormalities, is well treated with intramuscular benzathine penicillin in a normal host, despite a lack of "adequate" CNS penetration. Patients must also consent to and be able to tolerate lumbar puncture. These two criteria together form the most conservative guidelines for CSF examination in late latent syphilis.

Because nonpenicillin regimens have not been well documented to treat neurosyphilis, it is prudent to rule out asymptomatic neurosyphilis in patients with latent disease who would otherwise be treated with alternative therapy. Other evidence of late infection like cardiovascular or gummatous disease mandates an evaluation for neurosyphilis, as does concurrent HIV infection. Patients in whom the treatment of early syphilis has failed are at increased risk for CNS involvement and should undergo lumbar puncture before retreatment. The Centers for Disease Control and Prevention (CDC) recommends that patients who have a VDRL or RPR titer of 1:32 or greater after a year of infection should also be evaluated with a lumbar puncture, as they may also be at increased risk for neurosyphilis.[25]

Diagnosing Asymptomatic Neurosyphilis

Once the decision to screen is made, the immediate problem is to identify asymptomatic neurosyphilis if it is present. Unfortunately, no practical treatment standard exists for diagnosing this disorder. Instead, we are faced with using a variety of tests in combination, none with ideal sensitivity and specificity (Table 4). There is consensus in the literature that a positive serum treponemal antibody test is absolutely required for making the diagnosis.[7] Unfortunately, treponemal antibody in the CSF is not diagnostic for neurosyphilis, as it may represent only passive diffusion of treponemal antibody from the blood into the CSF rather than active CNS infection.[26]

TABLE 4.—*Criteria for the Diagnosis of Neurosyphilis*

Reactive serum treponemal antibody test (FTA-ABS or MHA-TP)
Reactive cerebrospinal fluid (CSF) VDRL test*
CSF pleocytosis (>5 leukocytes × 10^6/liter) with or without elevated protein level

FTA-ABS = fluorescent treponemal antibody absorption, MHA-TP = microhemagglutination-*Treponema pallidum*

*In some instances, an unreactive CSF-VDRL test may be consistent with a diagnosis of neurosyphilis. See text.

The CSF-VDRL test is extremely specific: a patient who has a positive test should be treated for neurosyphilis. The sensitivity of this test, however, varies in the literature from 30% to 90%.[5,10] Why is this range so broad? Historically, the sensitivity of the CSF-VDRL test has been assessed in patients with symptomatic neurosyphilis. Unfortunately, during the period when neurosyphilis was relatively prevalent and the classic studies were carried out, several common neurologic syndromes were not well understood. In these studies, neurologic symptoms were likely ascribed to neurosyphilis in patients with other evidence of syphilis infection.[27] For this reason, patients with carotid artery disease, viral meningoencephalitis, lacunar syndromes, or basilar artery insufficiency, to name a few unrecognized diagnoses, who had serologic evidence of syphilis but a negative CSF-VDRL test, were undoubtedly labeled with "seronegative" neurosyphilis. The VDRL test, then, may be much more sensitive than historical data suggest; in fact, some experts require a CSF-VDRL test for the diagnosis of asymptomatic or symptomatic neurosyphilis. It is well known, however, that *T pallidum* can be isolated from CSF that is negative on the VDRL test[5]; in addition, cases have been described of patients with a negative CSF-VDRL test who have clinical evidence of neurosyphilis and who respond to penicillin therapy. The CSF-VDRL sensitivity is, therefore, almost certainly better than reported in the historical literature, but likely not 100%.

Finally, CSF pleocytosis and an elevated protein level are nonspecific findings that may be associated with neurosyphilis. Many patients with primary and secondary syphilis manifest CSF abnormalities early on; those with abnormalities persisting into late latency are at risk for progressing to symptomatic neurosyphilis.[6] Therefore, unexplained CSF pleocytosis or elevated protein concentration in a patient with serologic evidence of syphilis should be taken as presumptive evidence of asymptomatic neurosyphilis.

Symptomatic Neurosyphilis

How do we determine if neurologic abnormalities in a patient with evidence of syphilis infection actually represent neurosyphilis? First, the diagnosis requires the presence of serum treponemal antibody. The CSF-VDRL test, as discussed earlier, is specific and reasonably sensitive in these patients. Unlike in patients with asymptomatic neurosyphilis, however, CSF pleocytosis with or without an elevated CSF protein level should be present if the disease is active.[7,27] In fact, without both a positive CSF-VDRL test and CSF pleocytosis, active neurosyphilis should be diagnosed only after a thorough search for alternative diagnoses. A symptomatic patient with unexplained CSF pleocytosis and a positive serum treponemal antibody test without a positive CSF-VDRL test could be treated presumptively for neurosyphilis, though that diagnosis must be a cautious one in such a patient.[27]

Manifestations of Neurosyphilis

As pointed out in a review, neurosyphilis is not one disease, but a collection of syndromes that span all stages of syphilis, from within weeks of infection to 50 or more years.[7] The classic late manifestations of neurosyphilis, general paresis and tabes dorsalis, are now exceedingly uncommon. Although also rare, the early forms—syphilitic meningitis and meningovascular syphilis—are currently of greater concern, especially in patients with HIV infection.

Syphilitic meningitis occurs in patients with early infection; in 10% of patients, it develops while the rash of secondary syphilis is still present.[7] Its symptoms are those of meningitis: headache, confusion, and meningeal signs. Cranial nerve abnormalities may occur and typically involve cranial nerves III, V, or VIII. These symptoms generally resolve even if untreated, although patients may be left with cranial nerve palsies. Worse, such patients remain at risk for the recrudescence of neurosyphilis. With treatment, symptoms will resolve in a few days to weeks. Meningovascular syphilis also occurs early, usually in the first months to a few years after infection. Unlike stroke syndromes, which usually occur with full neurologic deficits at the outset, meningovascular syphilis may present with a prodrome of nonspecific symptoms such as headache, psychiatric changes, or vertigo before focal neurologic deficits appear.[7]

Late neurosyphilis was common before the development of penicillin: in the early part of this century, general paresis of the insane accounted for 20% of psychiatric hospital admissions in the United States. Its symptoms are those of dementia and psychosis, and if untreated, it is fatal within months to a few years. Tabes dorsalis also occurs late in infection and is characterized by a triad of symptoms (lightning pains, dysuria, and ataxia) and a triad of signs (Argyll Robertson pupil, loss of reflexes, and loss of proprioception). Both general paresis and tabes dorsalis are extremely uncommon since the introduction of penicillin.

Treatment of Late Latent Syphilis and Neurosyphilis

Late latent syphilis is best treated with benzathine penicillin G, 2.4 million units given intramuscularly each week for three weeks (Table 5).[25] The use of doxycycline and erythromycin are less well studied; recommendations for their use in latent disease are

TABLE 5.—*Treatment of Late Latent Syphilis or Syphilis of Unknown Duration*

Therapy	*Regimen*
Recommended	
Benzathine penicillin G.....	2.4 million units IM as 1 dose/wk for 3 wk
For penicillin-allergic patients	
Doxycycline	100 mg orally 2 ×/day for 4 wk, or
Tetracycline.....	500 mg orally 4 ×/day for 4 wk

IM = intramuscularly

simply extensions of recommendations for treating early syphilis.

Penicillin, administered intravenously or intramuscularly, remains the drug of choice for treating neurosyphilis (Table 6).[25] The effectiveness of alternative therapies is unproved. Administering amoxicillin in high doses (2 grams 3 times a day) along with probenecid (500 mg 4 times a day) to raise drug concentrations appears effective in a small number of patients and may prove to be an outpatient treatment alternative.[28] Because of the large dosage required, this regimen can be difficult for patients to tolerate. Ceftriaxone sodium remains an unproven therapy to date, with notable rates of treatment failure reported in HIV-infected patients.[29]

How do we monitor the treatment response in patients with latent syphilis or neurosyphilis? As in early syphilis, the serum titer must be measured to ensure that it declines at least fourfold, although the decline is slower the longer the duration of infection. The titer may not revert to zero even with adequate treatment. Rising titers indicate treatment failure or reinfection.

In patients with neurosyphilis, follow-up CSF examinations should be done at six-month intervals over the first two years, or until the CSF becomes normal.[25] Resolving pleocytosis is generally the first measure of improvement and should occur over about six months.[30] Elevated protein levels, if present, will begin to decline during the first six months, but can take up to two years to return to normal. The CSF-VDRL titer should decline (fourfold within a year) if it is initially high, but it may take years to revert to negative.[30] A persistent, low CSF-VDRL titer after a course of treatment may warrant retreatment; however, if CSF pleocytosis and elevated protein levels have resolved and the serum VDRL titer is not increased, additional therapy is unlikely to be beneficial.[27]

TABLE 6.—*Recommended Treatment of Neurosyphilis**

Drug	*Regimen*
Aqueous penicillin G.....	2-4 million units IV every 4 hr, for 10-14 days, or
Procaine penicillin	2.4 million units IM a day, plus probenecid, 500 mg orally 4 ×/day, both for 10-14 days

IM = intramuscularly, IV = intravenously

*Some experts follow either regimen with 1 to 3 weekly dose(s) of benzathine penicillin G, 2.4 million units IM.

The goal of therapy for neurosyphilis, particularly general paresis and tabes dorsalis, is to halt the progression of disease. Symptoms of meningitis, and to some extent meningovascular syphilis, should resolve with therapy, but general paresis and tabes dorsalis are much less likely to abate. Neurologic signs or symptoms attributed to syphilis in the absence of CSF pleocytosis are unlikely to respond to therapy.[7]

Syphilis and Human Immunodeficiency Virus Infection

With the increasing prevalence of HIV as well as syphilis, the interaction of these two infections has become a topic of current interest and clinical importance. In studies controlled for known HIV risk factors such as number of sexual partners, male homosexual activity, and injection-drug use, syphilis emerges as an independent risk factor for HIV infection.[31] Not surprisingly, then, the prevalence of syphilis in patients with HIV infection is high: 14% to 36% in various studies, depending on the background rate in the community.[31,32]

A frequently noted concern is that the antibody response to syphilis may be delayed or impaired in HIV-infected patients. Are the serologic tests on which we rely for the diagnosis and follow-up of syphilis still useful in patients with HIV infection? A widely quoted report described the case of a patient with the acquired immunodeficiency syndrome (AIDS) who initially had seronegative secondary syphilis; a VDRL test did eventually become positive, although not until at least 20 days after the onset of a syphilitic rash.[33] Despite this report, there is little other evidence so far that seronegative syphilis poses an important diagnostic problem in patients with HIV.

Is the rate of false-positive serologic tests for syphilis substantially increased? Polyclonal B-cell activation is recognized to occur early in HIV infection, possibly leading to an increased rate of false-positive tests. A study of more than 4,800 patients found that the false-positive RPR rate in patients with HIV was about 4%, whereas in HIV-negative patients, the rate was slightly less than 1%.[11] Thus, although the number of false-positive tests does appear to be increased, the overall rate remains manageably low.

Other studies have found that higher titers of nontreponemal antibody develop in patients with HIV and early syphilis than in HIV-negative patients. A study from New York found a median RPR titer of 1:128 in a group of HIV-infected patients compared with 1:32 in a group of non–HIV-infected patients.[34] These higher titers have raised concern for the "prozone effect": false-negative serologic tests due to vast antibody excess. In such cases, positive serologic tests can be detected by diluting the specimen. Despite this concern, so far the prozone effect appears to be of predominantly theoretical rather than clinical importance in patients with HIV.

Finally, treponemal antibody seroreversion may be more frequent in patients with HIV. The rate of seroreversion was compared in patients without HIV, with

early asymptomatic HIV, and with symptomatic HIV, and it was found that the rate of seroreversion progressively increased with worsening immune function.[35] No HIV-negative patients lost the treponemal antibody response after treatment, but 7% with asymptomatic HIV and 38% with symptomatic HIV became seronegative. The clinical importance of this difference is unclear because all patients in the study had been treated, and it is known that healthy patients treated for syphilis may become treponemal antibody-negative.[19] Despite these caveats—a higher incidence of false-positive tests and higher rate of seroreversion after treatment—the serologic response to syphilis is generally preserved and remains useful in diagnosing syphilis in patients with HIV infection.

Clinical Manifestations of Syphilis in Patients Infected With the Human Immunodeficiency Virus

Are the clinical manifestations of syphilis altered in patients with HIV infection? Researchers in New York who evaluated patients with syphilis who did or did not have HIV infection found no significant differences in clinical presentation, course of disease, or response to treatment.[34] A number of studies, however, have reported the prevalence of neurosyphilis in HIV-infected patients. One remarkable study found that 9% of HIV-infected patients had a positive CSF-VDRL test; overall, 39% of the patients in this study had abnormal CSF findings that might be attributed to neurosyphilis.[36] In other studies, the prevalence of neurosyphilis (defined as a positive CSF-VDRL test) in unselected patients with HIV has ranged from 1.5% to 2%.[37,38] Reports of cases of symptomatic neurosyphilis in patients with HIV describe the manifestations of early neurosyphilis: meningitis with cranial nerve abnormalities and meningovascular syphilis with focal neurologic deficits, even polyradiculopathy.[39-41] Ocular involvement has been described, involving almost any part of the eye and including retinitis resembling cytomegalovirus infection. Cranial nerve VIII is also commonly involved with syphilitic meningitis. All these manifestations are well known to occur in non-immunocompromised patients; whether these neurologic syndromes are more severe in patients with HIV infection is unknown.

There is increasing evidence that HIV-infected patients may not respond as well as non-immunocompromised patients to standard treatment of early syphilis. In one study, three patients with secondary syphilis and HIV infection were treated appropriately for secondary syphilis with a single dose of benzathine penicillin.[5] All three had viable *T pallidum* recovered from the CSF after treatment. A recent review found that of 42 reported patients with HIV presenting with symptomatic neurosyphilis, 16 had received standard therapy with penicillin for earlier stages of syphilis.[42] Historically, the risk of early neurosyphilis ("neurorecurrence") is higher in partially treated patients. If standard therapy for early syphilis is more likely to fail for HIV-infected patients, the patients may be at increased risk for the development of early neurosyphilis after receiving usual treatment.[17]

The optimal evaluation of patients with HIV and early syphilis remains unclear. Because early asymptomatic CNS involvement is a risk factor for later symptomatic neurosyphilis, early CSF abnormalities may be important to recognize in patients infected with HIV. For this reason, some experts recommend lumbar puncture for all stages of syphilis in HIV-infected patients; others reserve CSF examination for patients with secondary or latent syphilis. Patients infected with HIV who have latent syphilis definitely require CSF examination to rule out neurosyphilis before treatment.[25]

The diagnosis of neurosyphilis is complicated in HIV-infected patients by the frequency of CSF abnormalities—pleocytosis and elevated protein levels—resulting from HIV infection itself.[43] It remains difficult to determine whether these nonspecific CSF findings should be attributed to neurosyphilis in HIV-infected patients with evidence of syphilis infection. Until better methods of diagnosis are developed, HIV-infected patients with evidence of syphilis and unexplained CSF pleocytosis or elevated protein levels, as well as those with a positive CSF-VDRL test, should be treated with a regimen appropriate for neurosyphilis.

Treatment of Syphilis in Patients Infected With the Human Immunodeficiency Virus

For HIV-infected patients with early syphilis, no change in standard therapy is currently recommended by the CDC. Some experts suggest treating with a more intensive antibiotic course early in the course of infection (such as 3 weekly doses of benzathine penicillin rather than a single dose), given evidence of treatment failures with standard therapy, although data to support or refute this approach are lacking.[42]

Penicillin remains the most reliable therapy for neurosyphilis; patients with a penicillin allergy should be desensitized for treatment. The use of ceftriaxone sodium cannot currently be recommended.[29] Although until recently, no treatment failures had been documented in HIV-infected patients who received standard penicillin therapy for neurosyphilis, a number of cases have now been reported in which such patients failed to respond to the recommended regimen.[44,45] Penicillin treatment of early syphilis had previously failed in some of the same patients. These reports strongly suggest that there may be no reliable cure for neurosyphilis in these patients.

Follow-up after the treatment of early syphilis consists of a clinical evaluation and serologic tests at intervals of 1, 2, 3, 6, 9, and 12 months to ensure that titers are declining appropriately—at least fourfold in 3 to 6 months. If the VDRL or RPR titer has not changed after six months, it is appropriate to reevaluate the patient, including examination of the CSF, before retreatment.

Evaluating the response to treatment of neurosyphilis requires the same measures, along with serial CSF examinations at six-month intervals over two years or

until CSF results return to normal. The appropriate rate of the resolution of CSF abnormalities in these patients is not established; generally, the same guidelines as for non–HIV-infected patients are followed: pleocytosis resolution over six months, with a slower decline in an elevated CSF protein level and the CSF-VDRL titer. Patients with persistently abnormal CSF values or inadequate serum RPR or VDRL titer response to treatment may be candidates for retreatment. Given the possibility of treatment failure, these patients require even greater than usual vigilance to ensure an adequate treatment response.

Conclusion

With its recent resurgence in the United States, syphilis has been transformed from a primarily historical disease to an important public health concern. The treatment of choice in all stages of infection is penicillin; doxycycline is a reasonable alternative for early syphilis. In patients with late latent disease, distinguishing asymptomatic neurosyphilis from late latency is necessary to determine the optimal treatment. Symptomatic neurosyphilis now presents mainly as meningitis and meningovascular syphilis, manifestations that may be more common in patients infected with HIV. Despite some limitations, serologic testing remains useful in patients with HIV infection. Finally, clinical and serologic follow-up is crucial in all patients, especially those with concurrent HIV infection, to detect treatment failures and thus prevent the occurrence of late complications.

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Conferences and Reviews

Health Care in Correctional Facilities

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More than 1.3 million adults are in correctional facilities, including jails and federal and state prisons, in the United States. Health care of the inmates is an integral component of correctional management. Health services in correctional facilities underwent dramatic improvements during the 1970s. Public policy trends beginning in the early 1980s substantially affected the demographics and health status of jail and prison populations and threatened earlier gains in the health care of inmates. Correctional health services are seldom considered in discussions about health policy and health care reform.

(Thorburn KM: Health care in correctional facilities. West J Med 1995; 163:560-564)

During the 1970s, prisoners successfully accessed federal courts to apply constitutional rights to their conditions of incarceration. In the case *Estelle v Gamble* (429 US97 [1976]), the United States Supreme Court concluded that "deliberate indifference to the serious medical needs of prisoners constitutes the 'unnecessary and wanton infliction of pain,'" in violation of the Eighth Amendment. This landmark case and others that followed established health care as a constitutional right of correctional inmates. (A glossary of terms used in this article is given in Figure 1.)

Organized medicine also became involved in correctional health care during the time that federal courts were calling for adequate health services. In 1972 the American Medical Association (AMA) surveyed health services in jails throughout the United States and found serious deficiencies.[1] The AMA received a grant from the Law Enforcement Assistance Administration to develop standards for correctional health services and to start a pilot project of accreditation programs through state medical associations. This program evolved to a free-standing accreditation group, the National Commission on Correctional Health Care, which continues to update standards for health services in jails, prisons, and juvenile facilities.[2-4] Other professional associations, including the American Public Health Association and the American Correctional Association, also have standards for correctional health services.[5,6]

The American Correctional Health Services Association was founded in 1975. It is a multidisciplinary membership organization comprising health professionals who work in correctional institutions. This professional organization has contributed to improvements in correctional health services through quality training opportunities, a communication network, and carefully considered policy statements.

The Burgeoning Correctional Population

Public policy trends in the 1980s caused setbacks to the improvements in correctional health services. Crime became a focus of legislators, who began to pass laws limiting judicial discretion in sentencing. The use of community-based intermediate sanctions became restricted, and there was more reliance on incarceration as the sole sanction for the conviction of criminal offenses.

The National Drug Control Strategy mandated long prison sentences for drug-law convictions, swelling prison populations, and lengthening stays.[7] The burgeoning prison and jail populations threatened the gains that had been made in correctional health services. The sheer numbers strained resources, especially as shrinking public funding bases during the late 1980s and early 1990s limited staff increases and equipment purchases. Health care facilities in jails and prisons grew more cramped and inadequate.[8] The growing number of drug offenders affected correctional health services as the incarcerated population became sicker and older.[8] An increasing percentage of women behind bars also affected the delivery of health services.[9,10]

Public policy decisions regarding the custodial management of mentally ill persons altered demands on correctional health services. During the 1970s, there was a trend to deinstitutionalize mentally ill people, a policy that closed many large public mental institutions. The objective of this policy was to return mentally ill people to their communities where they would receive an array of services for care and treatment. In many communities, these services did not materialize. Left to their own resources, mentally ill persons, with their bizarre behaviors, were brought into contact with law enforcement officials. Without public hospitals, jail may be the only institution in which to place mentally ill persons after charges stemming from illness-induced behaviors.[11-13]

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
AMA = American Medical Association
HIV = human immunodeficiency virus

Correctional Health Services

Before the upsurge in the correctional population in the 1980s, incarcerated persons were almost exclusively young and male. Men in their 20s and 30s were the lowest users of health services in the community. Their health care needs generally arose from trauma or acute self-limited illnesses.[14] Health care systems built on "access by demand" served their needs. Most correctional health services were organized as "sick call," a system of request for care of a specific medical problem and triage to the appropriate level of care.

In contrast, correctional health services today provide care for a large number of persons infected with the human immunodeficiency virus (HIV) and who have the acquired immunodeficiency syndrome (AIDS), tuberculosis, and other chronic infections,[15] as well as diseases that are more prevalent in aging groups, such as hypertension, ischemic heart disease, and emphysema.[16,17] The demand for gynecologic and prenatal services in jails and prisons grows as the number of incarcerated women increases.[18] Mentally ill inmates may be unable to express their health care needs, requiring prospective screening and identification. Oral health is another major concern among correctional inmates.[19,20] Sick call is not an appropriate delivery system for groups with high rates of chronic illness or for those at risk for diseases requiring screening for early diagnosis and prevention.

The demographic changes among inmate populations, including their health status, have made it necessary to remodel the delivery of correctional health services to more prospective interventions than sick call. Health services begin at admission to the facility, with screening to identify inmates with immediate or ongoing treatment needs, preexisting health conditions, or medical problems that might endanger the population and to provide baseline health information on inmates in custody. Health screening during admission is well established in all standards for correctional health services,[2-6] but other prospective and scheduled interventions are less developed.

Some of the program requirements in correctional health care systems include public health services, such as immunization programs, infection control, communicable disease surveillance, and health education. The care of chronically ill persons requires scheduled monitoring. These needs challenge correctional health care systems because inmates tend to move frequently among institutions, and many providers are involved in their care.

A review of some of the common medical problems of correctional inmates emphasizes the importance of systems of prospective and ongoing health care in correctional facilities.

Human Immunodeficiency Virus

The prevalence of HIV infection among state prison inmates was estimated to be 2.2% in 1991.[7] The rate varies widely among correctional systems, reflecting the rate among injection-drug users in the community, but all prison systems experience the HIV epidemic. The median incidence of AIDS among correctional inmates in 1992 was more than ten times higher than that among the general population.[21]

The challenge of managing HIV infection in the correctional environment extends beyond health services. Correctional systems struggle with issues of mandatory HIV testing; sharing or protecting information about HIV-infected prisoners; housing; terminal care; early-intervention treatment; prisoner access to investigational drug trials; HIV-prevention education,

Glossary

Community-based intermediate sanctions: penalties for criminal offenses that do not involve incarceration. A commonly applied intermediate sanction is probation: conditional release to the community with monitoring by court-appointed officers.

Corrections or correctional facilities: a generic term for institutions that originated during an era when public policy designated rehabilitation as the principal goal of incarceration.

Jails: correctional facilities that house pretrial inmates and inmates with short sentences of usually less than a year. Most jail systems are operated by local jurisdictions such as counties.

Mandatory sentences: statutorily mandated penalties have replaced indeterminate sentences that provided judges with a range of sanctions for a specific offense. If an indeterminate sentence involved incarceration, a parole board could review the offender's conduct and shorten the term of incarceration for good behavior. In contrast, mandatory sentences require fixed corrections penalties, usually incarceration with required minimum stays, for specific offenses and eliminate early releases for good behavior.

Prisons: correctional facilities that house convicted inmates who have sentences of more than a year or the maximum jail term. Prison systems are operated by states or the federal government.

Figure 1.—A glossary is provided of terms in this article that are used in the criminology and correctional health care fields.

including counseling before and after testing and condom distribution: and staff fears and education. Some issues are being resolved through litigation, but there is no standard protocol for HIV management in incarcerated populations.[21,22]

Recent studies emphasize the need for HIV-prevention efforts in correctional facilities.[23,24] Condom distribution to inmates to prevent the transmission of HIV and other sexually transmitted diseases is supported by many public health officials but opposed by most prison administrators.[25] The public health argument is that all effective interventions must be available to prevent disease transmission. These concerns are countered by the argument that providing condoms would condone sexual activity among inmates, which is illegal. The issue is important because of evidence of intraprison spread of HIV, despite the prohibition of behaviors associated with transmission.[26,27]

Another debate about the management of HIV infection among incarcerated persons is the issue of mandatory testing. Many jurisdictions require written consent before a person undergoes HIV antibody testing. Offenders, especially sex offenders, are often statutorily excluded from consent requirements and subjected to mandatory testing. Some correctional systems have mandatory HIV testing for their entire population or for identified groups at risk for infection. Cost, both for the tests and for early treatment of the newly identified infections, is a consideration in implementing this strategy.

In 1992, 16 state systems and the Federal Bureau of Prisons had mandatory testing programs. For incoming inmates undergoing mandatory testing, the rates of HIV infection in these systems ranged from 0.2% in Iowa to 3.2% in Rhode Island. State correctional systems with high rates of HIV infection, such as those in California, Florida, New York, and Illinois, have examined their rates through blind studies, but have not established mandatory testing programs.[21]

Other HIV assessment options include voluntary and diagnostic testing. Voluntary testing programs offer opportunities to identify infected inmates and to provide education before and after testing. In British Columbia provincial prisons, 91.3% of inmates participated in a voluntary testing project.[24] A study in the Maryland prison system achieved 47% acceptance of voluntary testing. When the participants were linked to blinded seroprevalence data, it was determined that voluntary testing identified 37% of HIV-infected inmates.[28] In Hawaii, all correctional facilities are anonymous test sites of the Department of Health. About 30% of the inmate population undergoes voluntary HIV testing annually (unpublished cumulative data through 1994).

Tuberculosis

From June 17 to August 8, 1991, four inmates from a single New York State correctional facility died of tuberculosis. Investigation of the outbreak revealed eight cases of active tuberculosis at the institution during the first 11 months of 1991, including one in a correctional officer. Two of the inmates had transferred from another state correctional facility where they received exposure from an inmate with multidrug-resistant tuberculosis. *Mycobacterium tuberculosis* isolates were resistant to isoniazid, rifampin, ethambutol, streptomycin, kanamycin, and ethionamide. No treatment was effective, and death occurred in an average of 25 days after active disease was diagnosed.[29,30] Epidemiologic analysis of the entire New York State prison system during that year identified a tuberculosis case rate of 156.2 per 100,000 inmates.[31]

California is another prison system in which there has been a well-investigated tuberculosis epidemic after three cases (1 employee and 2 inmates) were identified in a single institution in September and October 1991. The investigation revealed an annual incidence of 184 cases of tuberculosis per 100,000 inmates at the institution, more than ten times the annual incidence in California's general population (17.4 per 100,000). A new *M tuberculosis* infection rate was 5.9 per 100 person-years spent in prison.[32]

As the New York and California prison system outbreaks show, overcrowded institutions, often with a high proportion of immunosuppressed people, are fertile ground for the spread of tuberculosis. The situation is even graver where there are high rates of multidrug-resistant *M tuberculosis*. The rapid turnover of incarcerated populations, especially in jails; mass movements of inmates among crowded institutions; lack of appropriately ventilated facilities[33]; and prolonged drug regimens are challenges to implementing effective tuberculosis control programs in correctional institutions.

Tuberculosis control problems in correctional facilities are compounded by a lack of screening. According to a 1992 nationwide survey, 35% of prison systems and 48% of 31 large jail systems did not record *M tuberculosis* infection rates. The survey estimated that almost two thirds of prison systems did not do periodic tuberculosis screening.[34]

Aging

Longer mandatory prison sentences and restrictive release policies mean that the incarcerated population is aging. Humanitarian concerns, such as age and chronic illness, cannot be mitigating factors in sentencing. In some jurisdictions, elderly inmates are the fastest growing segment of the inmate population. In 1989 the average age of the United States prison population was 29.6 years, but about 5% was 50 years old or older.[35]

Aging is associated with higher rates of chronic illness. A study in Michigan found that 83% of inmates aged 50 or older had at least one chronic illness, and almost half had three or more chronic health problems.[36] The health status of elderly inmates is complicated by a susceptibility to infectious diseases associated with chronic illnesses, institutionalization, and high-risk behaviors.[37]

Prospective care, including screening for the early detection of chronic illnesses, is not a component of sick-call systems. Correctional health services must ensure continuing care of inmates with chronic illnesses as they move among institutions and into the community. Prison administrations are also faced with demands for special dietary and other programmatic needs for inmates with chronic illnesses.

Women's Health

Drug sentencing caused a rapid growth of the incarcerated female population. Between 1980 and 1989, there was a 202% increase in the number of women in prison compared with 112% for men.[9] In 1991, one woman in three was convicted of drug offenses compared with one in nine in 1986. Even with this dramatic growth, women comprised less than 6% of the prison population.[18]

Because women represent a small proportion of incarcerated people, their needs are difficult to meet in systems that are planned for male-dominated programs. Women require scheduled health care interventions, such as regular Pap smears, mammography, and prenatal care. Many incarcerated women have been sexually active with multiple partners and are at risk for cervical cancer and sexually transmitted diseases.[38] Yet, a 1992 survey of 85 state and federal prisons indicated that more than 15% did not have on-site gynecologic care.[18]

In 1991, 6% of women entered prison pregnant. During 1992, the prenatal clinic in the Los Angeles County jail system cared for 150 to 250 women at any one time (Tom Flannigan, RN, Sybil Brand Institution, oral communication, October 1992). The pregnancies often need intensive management because of risks such as drug use during the early stages.[39] Public policy in some jurisdictions hinders the access of incarcerated women to abortion services. Most programs do not have nurseries or mother-infant facilities, and new mothers must separate from their infants after one or two days in a hospital for the birth.[40]

Oral Health

At least 30% of correctional inmates require dental treatment beyond routine prophylaxis, and the needs are often extensive.[20,41] Dentists in correctional facilities work without assistants who would increase efficiency. Dental hygiene services are often included among the dentists' duties in lieu of hiring dental hygienists.

Serious oral disease and inadequate staffing impede attempts to provide comprehensive dental care. Correctional dental staffs find themselves in cycles of responding to dental emergencies or impending emergency conditions, leaving no time for periodontal or other preventive care. Restorative care, nonemergency oral surgery, and prosthodontic services are relegated to waiting lists that never diminish.[19,42]

Mental Health

The rate of serious mental illness—excluding substance abuse and personality disorders—in incarcerated populations has been estimated to range between 6% and 14%.[43] The rates tend to be higher in jails than in prisons, as local jurisdictions try to cope with mentally ill persons and inadequate community treatment resources.

Mentally ill persons are often arrested for minor infractions, such as trespassing, creating a nuisance, or failing to appear in court. The behaviors are attributable to the illness, but without treatment alternatives, the arrestee is diverted into the criminal justice system. Stays in the correctional system for these offenses are short. Once a mentally ill person returns to the community, without referral to services, the behavior recurs, and the return to jail becomes a revolving-door cycle.[12,44]

Inadequate staffing plagues correctional mental health programs that have often been organized to provide forensic evaluations rather than treatment services. Psychiatrists may be the sole treatment providers and have limited time to devote only to those inmates with the most serious disorders. Pharmacotherapy may be the only available mental health intervention, although many correctional inmates would benefit from counseling, substance abuse treatment, and other mental health modalities.[44]

Seriously mentally ill inmates in the correctional environment need more than clinical treatment services. They are vulnerable to abuse in the general correctional population. Special segregated housing and other programmatic needs confront prison administrations.[44]

Suicide

A study in the Maryland prison system found that suicide deaths among male inmates from 1979 to 1987 were significantly greater than in the community at large—39.6 suicides per 100,000 male inmates compared with 22 per 100,000.[45] Rates of suicide deaths may be even higher in jails.[46] Although the early hours of detention present great risk, suicide does not seem to be associated with particular temporal events in long-term incarceration.[45] Hanging is the most prevalent method of completed suicide in the correctional setting.

Death from suicide in correctional facilities should be preventable. A comprehensive program of suicide prevention requires procedures for identifying suicide potential, training, notification and referral capabilities, protective and safe environments, monitoring plans, and techniques to intervene in a suicide in progress.

Correctional Health Costs

The change in the demographics and health status of the incarcerated population during the 1980s affected correctional budgets. The average yearly cost of health care for a correctional inmate more than doubled between 1982 and 1989 from $906 to $1,848. A 1989 survey of prison health care budgets indicated that they represented an average of 9.5% of overall prison budgets, ranging from about 5% to 19%. The cost of health care for inmates incarcerated in the nation's prisons in 1989 was about $25 million.[47]

The Future

Public policies on crime, poverty, substance abuse, and other socioeconomic issues affect the health status of the incarcerated population. Current social policies create a mandate for public health programs and complex clinical services within correctional facilities. Most prisoners are discharged from the facilities, and their health should be protected for the sake of the larger community, if not to contribute to their rehabilitative potential.

Correctional health services represent a substantial segment of the nation's health care system. Public health and academic liaisons are needed if recent advances in correctional health care are going to be sustained, but integration into the broader health care community must be the goal. Correctional health care should be a consideration as our nation makes decisions about our health care system of the future.

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Epitomes

Important Advances in Clinical Medicine

Orthopedics

David B. Thordarson, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association, and the summaries were prepared under the direction of David B. Thordarson, MD, and the panel.

Orthopedic Implications of Tuberculosis

TUBERCULOSIS IS undergoing a resurgence in the United States, associated with the acquired immunodeficiency syndrome (AIDS) epidemic, the influx of immigrants from underdeveloped parts of the world, and perhaps some increased complacency in the medical community. About 15% of cases of infection with *Mycobacterium tuberculosis* are extrapulmonary, and of these, 9% to 10% involve the bones and joints. In the vast majority of cases, the organism is delivered to the skeletal system during lymphohematogenous dissemination from a pulmonary focus. The organism may lie dormant in the skeletal system for long periods after the initial dissemination before disease is detected and typically progresses from a focus in the epiphyseal region of the bone, where it may produce either chronic arthritis or osteomyelitis.

Tuberculous arthritis typically occurs as chronic monarthric (monoarticular) arthritis. The infection is slowly progressive. The knees, hips, ankles, and wrists are most often involved. Pain and swelling are common features of this form of arthritis, and years may pass before a diagnosis is established. Biopsy of the synovium will typically yield granulomas. Aspiration with the appropriate stain and culture is always necessary, but the initiation of treatment often requires a high index of suspicion, a positive tuberculin skin test, and sometimes a characteristic appearance on synovial biopsy. A positive smear culture is always a reassuring confirmation of the diagnosis.

Therapy now relies on the use of a four-drug combination for sensitive stains of *M tuberculosis*, at least for the first two months, followed by prolonged treatment with isoniazid and rifampin. Treatment durations of at least a year seem appropriate. Surgical debridement is unnecessary in all but advanced cases; results are excellent if the disease has not progressed. Advanced degrees of joint destruction before therapy is started lead to a poor prognosis.

Tuberculous osteomyelitis most commonly involves the spine (vertebral osteomyelitis or Pott's disease). The disease typically involves the intervertebral disc, leading to destruction of the disc and anterior wedging. The thoracic spine is most commonly involved, followed by the lumbar area. Pus may form and dissect into the neck, groin, buttocks, or other areas, and large paraspinous abscesses may occur. Characteristic roentgenographic changes can be seen with destruction of the disc space and bony erosion. Neurologic impairment and damage may occur if caseous or granulomatous material impinges on the cord.

The diagnosis is established through a bone biopsy and culture, either with a needle or with open surgical intervention. Treatment is again largely medical, although surgical treatment may be required to relieve pressure on the cord in patients with neurologic impairment or to stabilize bone. In general, paraspinous abscesses do not require drainage if they are tuberculous in origin and not associated with signs of neurologic compromise. Treatment should be extended for as long as two years. The results of therapy should be excellent if the disease is diagnosed early.

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Bone Graft Substitutes

BONE GRAFTING is commonly used to augment bone repair, with several approaches to reconstructing or replacing musculoskeletal defects. The autogenous grafts can be cancellous, nonvascularized cortical, or vascularized cortical. Because these grafts are associated with

several shortcomings, however, including an 8% incidence of substantial morbidity, alternatives to autogenous bone grafting have been developed. Grafting substitutes currently include cancellous and cortical allografts, ceramics, demineralized bone matrix, bone marrow, and composite grafts.

The bone grafting process uses three elements: osteogenesis, osteoinduction, and osteoconduction. Osteogenic cells have the potential to differentiate and facilitate the various stages of bone regeneration. Osteoconduction provides a matrix that is a nonviable scaffolding, conducive to bony ingrowth. Osteoinduction includes chemical or physical agents that induce the various stages of bone regeneration. Each of the graft substitutes has one or more of these components.

Allografts can provide structure and an osteoconductive environment. They provide local growth factors and osteogenic cells. Structural allografts induce a modified rejection response from the host that varies from massive dissolution of the graft to benign neglect. These grafts have a substantial rate of nonunion (>10%), fracture (>10%), and infection (15% to 20%). In addition, the grafts can carry hepatitis and the human immunodeficiency virus (HIV; 1 per 1 million cases).

Ceramics are grouped into hydroxyapatite and tricalcium phosphate. Hydroxyapatite is similar to the human bone mineral phase, with the exception that the ceramic does not include the many imperfections of human bone. It is turned over slowly (>10 years). Tricalcium phosphate is converted in the body in part to hydroxyapatite. It is more easily resorbed, but large segments of this ceramic still last beyond five years. Synthesized ceramics are brittle, lack direct porous connectivity, need bony ingrowth to improve their mechanical properties, and require either osteogenic cells or growth factors to succeed. A new form of ceramic synthesized from coral has the three-dimensional microstructure of bone. These coralline ceramics are commercially available with average pore sizes of 500 and 200 μm.

Demineralized bone matrix removes the mineral phase and exposes the underlying bone collagen and growth factors, most notably bone morphogenetic protein. These grafts have no structural capability but provide sufficient bone morphogenetic protein to osteoinduce bone in osseous defects.

Bone marrow has a substantial number of osteogenic cells that are capable of providing bony regeneration. It has been demonstrated that 150 cm^3 of bone marrow can successfully heal established tibial nonunions. Most researchers in the field of bone grafting urge the coinsertion of bone marrow with any of the bone graft alternatives.

Composite grafts combine hydroxyapatite and tricalcium phosphate with bone marrow to heal bone defects. In a randomized controlled study, Collagraft performed as well as autogenous bone graft in repairing long-bone fractures. When the grafting site is compromised, a composite of particulate ceramic, bone marrow, and demineralized bone matrix that incorporates all the regenerative elements may be just as effective as autogenous cancellous bone graft.

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Arthroscopic Subacromial Decompression for the Shoulder Impingement Syndrome

A PAINFUL SHOULDER IMPINGEMENT syndrome has become a more meaningful problem in industrialized society because many occupations now necessitate prolonged periods of overhead activity. In this position, the shoulder is vulnerable to injury, especially the superior glenohumeral and inferior acromial structures. Repetitive damage can lead to the progression of the disease and eventual permanent shoulder disability. Most patients, however, respond to a simple treatment program aimed at modifying their activity, reducing inflammation, and strengthening the shoulder muscles.

The impingement syndrome of the shoulder compromises the space between the coracoacromial arch and the humeral head, resulting in soft tissue injury. The anatomic structures of the coracoacromial arch make up a roof over the humerus and include the coracoid, the coracoacromial ligament, the acromioclavicular joint, and the acromion. The subacromial bursa, the supraspinatus tendon, and the tendon of the long head of the biceps brachii are most commonly injured by the impingement syndrome. Forward flexion and internal rotation of the humerus bring these structures under the coracoacromial arch. This is especially true when the space is further compromised by anterior acromial osteophytes. It is also possible that persons with an acromial undersurface that is downward curved or hooked may be predisposed to the impingement syndrome.

Patients with the impingement syndrome initially have pain when they reach upward. Often there is also pain with motion behind the back, as occurs when reaching into the back pocket of pants. Athletes have specific complaints, and throwing a baseball provides a good model for all overhead throwing sports. Pitchers complain of pain in the anterior shoulder during the acceleration phase or sometimes the follow-through. Initially the pain subsides after a short rest, but pain may become relentless if the offending activity is not stopped. The pain is especially intense with forward flexion and internal rotation. Physical examination reveals tenderness with palpation of the anterior acromion, and the Neer impingement maneuver reveals pain during passive forward flexion of the shoulder. Irritation of the rotator cuff may be reproduced by pain and weakness with specific strength testing. It is especially helpful to infuse 10 ml of lidocaine into the subacromial bursa and then to repeat the Neer impingement test. If the impingement syndrome is the sole problem, there should be a 70% to 100% diminution of the pain and normal rotator cuff strength.

An early impingement syndrome is reversible with rest, nonsteroidal anti-inflammatory medications, and rotator cuff-strengthening exercises done with the arm at the side. In more severe, chronic cases, administering steroid into the subacromial bursa is helpful in decreasing inflammation. Overhead activities should be restricted until symptoms abate. Most patients have a favorable response to nonoperative treatment for six months, but in unusual cases with persistent shoulder pain, operative decompression is efficacious.

Last, when the shoulder impingement syndrome is manifest, it is important to look for other, often-associated disorders. Rotator cuff tear, glenohumeral instability, and generalized ligamentous laxity can be the primary problems in these patients. An accurate diagnosis and treatment aimed at the complete shoulder injury are required for a return to pain-free function.

Open acromioplasty to decompress the space between the coracoacromial arch and the humeral head has had satisfying results. Now arthroscopic subacromial decompression has been championed as an alternative to the open procedure because of decreased morbidity, full visualization of the space without detachment of the deltoid origin, an early return to normal activities, and the ease with which the operation can be done on an outpatient basis. Results compared with those of open acromioplasty have been favorable concerning the elimination of pain, the return of shoulder function, strength, and range of motion, and patients' satisfaction. This technique is generally more technically demanding than the open procedure, however, and failures have been reported, usually due to inadequate resection. For this reason, evaluating for acromial disease before the operation, adequately visualizing the subacromial space, using a precise technique, and determining the adequacy of resection are all important for a successful result.

Recent investigations have confirmed long-held suspicions concerning the importance of the coracoacromial arch. It is likely not the "appendix of the shoulder," and complete resection of the coracoacromial arch may predispose the shoulder to glenohumeral injury, such as subtle instability or rotator cuff injury. For this reason, future areas of research include examining the role of the coracoacromial arch in normal shoulder function and determining the indications and technique of partial resection.

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Anterior Cruciate Ligament Repair in Children

INCREASED PARTICIPATION by youngsters in organized sports has resulted in an increased incidence of anterior cruciate ligament injuries in skeletally immature persons. The long-term outcome of nonoperative, conservatively treated, unstable anterior cruciate ligaments in children is similar to that in adults. A large percentage will continue to have episodes of swelling, giving way, catching, and locking. This results in meniscal and cartilaginous disease.

Twisting, deceleration, contact, or noncontact injuries are common in these persons. Hemarthrosis is usually present on examination. This, coupled with a positive Lachman sign and a positive anterior drawer sign, makes the diagnosis. The Lachman test is performed by applying anterior pull to the fibia with one hand while the femur is stabilized with the other. The patient should be supine and the knee flexed at 30 degrees. The pivot shift sign may be present but is often difficult to elicit in the acute stage. Meniscal tears are commonly seen in association with anterior cruciate ligament tears, similar to the case in adults.

X-ray films are important to diagnose pull-off fractures and to evaluate the distal femoral and proximal tibial growth plates. Magnetic resonance imaging, although not necessary to diagnose an anterior cruciate tear, can be used to reveal meniscal disease in those electing a nonoperative, conservative approach. If meniscal tears are identified, a more aggressive surgical approach should be considered. Nonoperative management of these patients results in the high likelihood of subsequent bouts of giving way, catching, and locking. In patients without meniscal tears, bracing and restricting activity until the growth plate closes are an option.

Surgical treatment remains controversial. Adolescents within six months of epiphyseal closure can undergo intra-articular anterior cruciate ligament reconstruction without substantial risk of leg-length inequality or angular deformity. The younger the child, however, the greater the risks of epiphyseal complication. Intra-articular grafts, avoiding both growth plates by passing over the front of the tibia and over the top of the femur, have been described. Similarly, grafts through the central portion of the tibia to minimize tibial epiphyseal changes and then over the top of the femur have also been reported. These techniques come from large centers but with a small number of patients. Physicians who see only an occasional case might be wise to use a more conservative surgical approach or to make the appropriate referral until more information is obtained in this regard.

All agree, however, that meniscal tears in young patients should be repaired if at all possible. Meniscal repairs with extra-articular tenodesis or bracing until the epiphyses approach closure, though not optimal, are an acceptable conservative surgical approach at this time. This should be coupled with strong advice to curtail high-risk activities such as football, volleyball, and skiing until

the growth plate closes and a strong intra-articular graft can be placed.

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The Ilizarov Method

TWENTY YEARS AGO there was a resurgence throughout Europe and the United States in the use of external fixation for the management of fractures and limb deformities. Advancements in materials and techniques have reduced the soft tissue complications previously precluding the use of this method.

Simultaneously in Kurgan, in what was then the Soviet Union, G. A. Ilizarov developed his technique of distraction osteogenesis. This important advancement facilitated limb lengthening, eliminating many of the complications and decreasing the amount of surgical intervention. Ilizarov pioneered the use of a tissue-sparing, cortical osteotomy-osteoclasis technique. This technique preserves the osteogenic elements in the limb. Ilizarov advocated a delay of several days before the initiation of distraction to allow the creation of a preliminary callus that could then be lengthened. He perfected the high-frequency, small-step distraction rhythm that permitted good-quality bone to regenerate and decreased soft tissue complications such as nerve and vessel injury.

This technique produces good-quality bone formation, minimizing the prevalence of nonunion (requiring further bone grafting) or premature consolidation of the lengthened segment (requiring osteotomy and osteoclasis to be repeated). Limb-segment lengthening of as much as 140% is now not only possible, but commonplace.

As the Ilizarov methods were learned in Europe and the United States, advancements in materials and external fixator biomechanics quickly modified the technique. This expanded the indications for the treatment of congenital and acquired limb deficiencies. Different external fixation configurations, modifying the ring fixator to uniplanar and biplanar frames and adding transfixion pins and half pins to the wire fixation methods, are now standard.

Complications still interfere with the successful management of limb deficiencies. These complications are predictable enough to have changed the nomenclature in the limb-lengthening literature. Complications that can be treated and do not alter the predicted results are referred to as "problems." Only those complications that alter the predicted outcome are truly "complications." Future trends to improve the Ilizarov method will reduce the complication rate. The goals will be to prevent pin-track infection and osteomyelitis, premature or delayed consolidation of bone, angular or axial deviation of the regenerate bone, joint contracture or instability, neurovascular compromise, and psychological adjustment reactions.

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Necrotizing Soft Tissue Infections

NECROTIZING SOFT TISSUE INFECTIONS have recently received substantial publicity in the lay press. These infections present as a variety of clinical, microbiologic, and pathologic syndromes that have received a confusing array of names, including hemolytic streptococcal gangrene, postoperative bacterial synergistic gangrene, Fournier's gangrene, monomicrobial necrotizing cellulitis, nonclostridial anaerobic cellulitis, gram-negative synergistic necrotizing cellulitis, and necrotizing fasciitis.

The hallmark of all these syndromes is infection of the subcutaneous tissue and fascia that produces necrosis, with relative sparing of the muscle. Differentiating between these syndromes clinically is often impossible, and some have suggested abandoning attempts at classification and adopting a common approach to all of them.

Necrotizing soft tissue infection remains a relatively uncommon disease. Although these infections can affect any part of the body, the extremities are most commonly affected. Patients often have underlying diseases, such as diabetes mellitus, injection drug use, chronic alcohol abuse, or peripheral vascular disease. Many cases occur in the postoperative period, especially after an intra-abdominal operation.

Necrotizing soft tissue infections may be due to either a monomicrobial or a polymicrobial process. Although group A streptococci are the most common cause of a monomicrobial infection, other organisms may cause similar syndromes, including *Vibrio vulnificus*, *Clostridium perfringens*, and fungi such as *Rhizopus*, *Mucor*, and *Absidia* species. Polymicrobial infections usually involve a combination of streptococcal species, *Staphylococcus aureus*, members of the Enterobacteriaceae, and anaerobes. Because these infections spread rapidly and are devastating and life-threatening, early diagnosis and aggressive therapy are keys to successful treatment. The difficulty is that, early in their course, necrotizing infections can appear similar to nonoperative cellulitis. Thus, early diagnosis depends on a high index of suspicion for the disease. Clinical signs suggestive of a necrotizing infection include edema that extends beyond the area of skin erythema, the absence of lymphangitis or lymphadenitis, the presence of gas in the soft tissues and skin vesicles, and progression to focal ecchymoses or skin necrosis.

Once the diagnosis of a necrotizing infection is suspected, prompt and aggressive treatment is essential.

Early radical debridement of all necrotic and ischemic tissue remains the most important aspect of treatment. Empiric, broad-spectrum antibiotic therapy is an important adjunct to aggressive debridement and can later be tailored, based on the results of cultures of surgical specimens. A single agent such as imipenem or the combination of piperacillin sodium and tazobactam sodium could be used, although recent literature suggests that the use of clindamycin phosphate may be more effective than penicillin in patients with severe infections caused by group A streptococci. The efficacy of hyperbaric oxygen therapy remains unproved.

The mortality of necrotizing soft tissue infections is high. Reported mortality in published series ranges from 9% to 64%, with a cumulative mortality in reports over the past 30 years of 38%. This high mortality can be reduced only by increased awareness by physicians of this disorder, resulting in early diagnosis, early aggressive debridement, broad-spectrum antibiotic therapy, and aggressive wound care.

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Women's Shoe Wear and Foot Disorders

FOREFOOT ABNORMALITIES occur predominantly in shoe-wearing societies. In the United States, it is estimated that 43 million persons yearly have foot complaints and that a third of these eventually seek medical care. The incidence of foot problems increases with increasing age. Footwear had been indirectly implicated as the cause of orthopedic forefoot problems in western societies. Published studies regarding societies that do not wear shoes demonstrate that forefoot problems are relatively uncommon. Unshod natives from Pacific Rim countries and Africa substantiate the fact that these populations have relatively few foot problems. Also, as these populations age, there does not appear to be an increase in the incidence of forefoot problems. Heretofore, there has been a paucity of information regarding the incidence of these problems in men compared with women.

A review of the number of surgical procedures done over a 15-year period showed that 87% of the forefoot procedures were in women. There was an equal incidence in both men and women of surgical procedures such as ankle fusions and ankle fractures, problems that are obviously not related to constricting shoe wear. In regard to specific diagnoses, women again had a much higher frequency of surgical procedures: hallux valgus procedures, 94%; hammertoe repairs, 81%; neuroma excisions, 89%; and bunionette corrections, 90%. With increasing age, the frequency of surgical correction increased as well. The fourth, fifth, and sixth decades were the most common age group for the surgical correction of these problems.

A conservative estimate for physician and hospital fees and time lost from work following forefoot surgical reconstruction is $2 to $3 billion a year. Although some of these procedures may be unavoidable, many may be prevented with the use of roomy, comfortable footwear.

The solution for many of these patients is to wear roomy shoes. Patient education is the key to success. The forefoot tends to spread with age, and patients cannot wear the same shoes that they wore when they were 20 years old. In a survey of 356 healthy women, 80% had foot pain or deformity. About 88% of those examined wore shoes that were too narrow by at least 13 mm (0.5 in). Most women's feet are about 8.25 to 10 cm (3¼ to 4 in) wide, although many fashionable shoes are available only in an 8-cm (3-in) width. Shoes may be stretched to accommodate bony prominences. Purchasing shoes that have more forefoot width can substantially lessen the amount of forefoot discomfort.

Lowering the heel height can have an important effect on patient comfort as well. A 2-cm (¾-in) heel increases forefoot plantar pressure by 22%; a 5-cm (2-in) heel increases plantar pressure by 57%, and an 8.25-cm (3¼-in) heel increases pressure by 76%. Initially this pressure may cause pain, but in time, may lead to hammertoe, neuroma, bunionette, and bunion formation. Obviously, high-fashion shoes cause increased pressure and pain in the forefoot, and with time, permanent deformities may occur. Lowering the heel height decreases not only side-to-side pressure, but also the pressure in the forefoot as the foot slides downward into the toe box.

Wearing shoes that hold the foot securely in place will help patients who have a complaint of a wide forefoot and a narrow heel. Lace-up, sling-back, or T-strap styles will help to hold the foot in place.

It is helpful to have a list of shoe stores where roomy shoes can be purchased. Questioning patients about where they have purchased a reasonably roomy shoe that is fashionable in appearance is a good way to keep a current list. Women on physicians' office staff can also help with gathering information about shoe stores that have reasonable shoes.

Patients should be warned that a "break-in" period is not a good idea because it is a period when the forefoot is compressed and constricted within a tight toe box. A patient should refuse to buy a pair of shoes that are tight, constricting, or uncomfortable.

It is important to make women aware of the damage associated with ill-fitting footwear. Increased public awareness is an important step in reducing the incidence of forefoot problems in women. The "emancipation" of women's feet will not occur rapidly, but physicians can take an active role in counseling and educating their patients regarding the ill effects of high-fashion footwear.

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Treatment of Fractures of the Femur in Children and Adolescents

ALTHOUGH THE STANDARD OF CARE in the treatment of femur fractures in adults is intramedullary nailing, treatment in children and adolescents is age-based and has evolved in recent years. The exact treatment regimen depends on the growth remaining, the size of the patient, the time to fracture healing, the remodeling potential of the fracture, and social factors, including parental work schedules, the extent of daily care needed for the child, and time missed from school, to name a few.

The causes of femur fractures in children younger than 4 years is related to abuse in 30%, high-energy trauma in 9%, simple trauma in 49%, and disease in 12%. In patients older than 4 years, most are trauma-related. Signs of abuse need to be recognized, however, and include an unreasonable history, a delay in treatment, and many unexplained injuries.

The treatment of most fractures of the femur in children younger than 6 years is the immediate application of a spica cast if the fracture is stable. In infants younger than 6 months, a Pavlik harness or a splint can be used for stable fractures. The "telescope test" can be used for determining the stability of pediatric femur fractures. Patients with suspected abuse should be admitted, placed in traction, and observed until a cause can be determined. The spica cast can be applied in the emergency department or cast room under sedation or general anesthesia, depending on the patient's need and the surgeon's preference.

Acceptable limits of alignment include 20 degrees varus or valgus and 1.5 cm of shortening. Correct rotational alignment is preferred. Children with multiple trauma or open injuries should be considered for surgical stabilization, depending on the size of the patient and the nature of the injuries.

Children aged 6 through 12 represent the group in which treatment methods have recently evolved. The standard of care continues to be traction, which can be skin traction or 90-degree–90-degree femoral pin traction, followed by spica cast. Reasons for considering other alternatives in patients with isolated femoral shaft fractures include shortening the hospital stay, improving the outcome, returning the patient to school and the parents to work, cost savings, and various social concerns.

The time in traction for children in this age group averages 2 to 4 weeks, followed by 8 to 12 weeks in a cast. This may result in a weak quadriceps, a stiff knee, and loss of alignment. There is renewed debate regarding acceptable limits of shortening and potential for "overgrowth" and remodeling in this age children.

Cost savings involve not just the hospital stay, but also time off work for parents and nursing needs at home.

Options for alternative treatment include external fixation, plate fixation, and intramedullary nailing with rigid or flexible nails. Any method can give satisfactory results. The particular method must be individually chosen, based on the physician's experience and the patient's needs. With improved devices, external fixation has become the preferred method in this age child for many physicians. Advantages include adjustability, ability to maintain desired reduction, ability to allow immediate weight bearing, an early return to school, decreasing hospital stays to less than a week, and improved quadriceps and knee function.

Intramedullary nailing with insertion through the proximal femur carries a high complication rate in this age group, with many reports of greater trochanteric overgrowth and avascular necrosis of the femoral head. Small flexible nails inserted from the distal femur are preferred by some surgeons, and initial reports show promise. Plate fixation allows anatomic reduction, but is not a mechanically favored device and leads to problems with overgrowth. Nevertheless, several series document a low complication rate with this method. Complications with all methods of internal fixation include hardware failure, infection, neurovascular injury, and hypertrophic scarring. The need for hardware removal must also be considered.

Adolescents older than 13 years can be treated as adults. Preferred treatment is anatomic reduction and stabilization with an intramedullary rod. Until physeal closure, the risk of avascular necrosis remains. Modifications in standard technique seem to reduce this risk, but prospective studies are not yet completed. For those unwilling to accept the risks associated with intramedullary nailing, traction followed by a spica cast or cast brace remains an option. Treatment times with these techniques can be prolonged and can lead to knee stiffness and unacceptable alignment and shortening after fracture union in as many as 20%. Other options in this age group include external fixation and plating.

Decision making in the treatment of children and adolescents with femoral shaft fractures continues to evolve. Treatment is age-related, and many factors need to be considered when choosing treatment for any individual patient.

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Surgical Indications for Spinal Instrumentation in Degenerative Diseases

INTERNAL FIXATION helps obtain a fusion and decrease the pseudarthrosis rate, maintain alignment, reduce deformities, stabilize the spine, and open neural foramina, particularly in patients with spinal stenosis, degenerative spondylolisthesis, or scoliosis. Lumbar segmental fixation is also particularly useful in patients with osteoporosis and where there is a lack of lamina available for conventional fixation techniques. Traditional posterior fixation systems that distract the lumbar motion segments—for example, Harrington or Knodt rods—lead to lumbar kyphosis, require intact laminae, and invade the canal. Pedicle-based segmental fixation improves torsional stability and helps maintain lumbar lordosis. The number of instrumented vertebrae is reduced, thereby preserving distal or proximal motion segments. This may reduce the future incidence of low-back pain.

More important than the decision to use instruments, however, is the choice to fuse. Fusions are indicated when a laminectomy is being considered for several reasons: treating degenerative conditions with one segment translation at motions greater than 4 degrees, stenosis with scoliosis, lateral slip, or surgical revision of the lumbar spine. In addition to these general recommendations, fusion should be considered when decompressions lead to the removal of the equivalent of one facet or if there are no large, bridging osteophytes present to stabilize the spine after a long or a wide decompression. In a prospective clinical study evaluating 124 patients undergoing lumbar fusions for degenerative conditions, the fusion rate greatly increased when rigid segmental fixation was used to supplement the fusion. In patients with in situ fusions, 71% had good to excellent clinical results, and 65% were fused. Those with semirigid pedicle instrumentation and bilateral, lateral autograft fusion reported good to excellent results in 89%, with a 77% fusion rate. The best results were observed in those who had a rigid pedicle screw-based system inserted to supplement the fusion. In this group, 95% reported good to excellent results, and a 95% fusion rate was achieved.

A recent meta-analysis evaluating available data in the literature related to the surgical treatment of patients with leg symptoms related to degenerative spondylolisthesis showed that patient satisfaction improves when spinal fusion is performed, and the fusion rate is enhanced when spinal instrumentation is used to supplement the fusion.

A large retrospective study involving 314 physicians and 2,177 patients who had pedicle screw placement for degenerative spondylolisthesis was reported in the literature and to a Food and Drug Administration (FDA) scientific advisory panel. In this study also, 456 patients had noninstrumented surgical fusions for degenerative spondylolisthesis (in situ control). Compared with the controls, patients with pedicle screw-based systems had a significantly higher rate of fusion (89% versus 70%), spinal alignment and clinical outcomes improved, and there was less pain, better function, and greater neurologic recovery. The rates of complications, reoperations, and deaths were similar in the two groups. A failure to place the pedicle screws in the correct location may lead to a neurologic deficit and a loss of fixation. The incidence of this complication decreases with experience, however. Implant breakage occurs, but in the retrospective cohort study, the reported rate was less than 1%. The infection rate with instrumented fusions is about two times higher than in the in situ group. The cost of the procedure is higher when instrumentation is used (increased blood loss, increased operative time, and the instrumentation itself), but this should be weighed against the improved function, increased fusion rate, and increased clinical success with an earlier return to work.

Instrumentation when used appropriately in degenerative conditions of the spine leads to a higher fusion rate. The relative indications for instrumentation include revision operations, cases of degenerative spondylolisthesis, fusion over multiple levels, scoliosis, stenosis with scoliosis or lateral slip or in cases where iatrogenic instability is created at the time of an operation. Of note, bone screws placed in the pedicle have not been cleared for this use by the FDA. Screws, as bone screws, are cleared for use in bone. Some companies have specific clearances to advertise and market their devices as pedicle screws for use in the treatment of grade 3 or 4 spondylolisthesis of L-5 over S-1, when used in conjunction with a posterolateral autograft fusion, with plans to remove the device after fusion is obtained.

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ADVISORY PANEL TO THE SECTION ON ORTHOPEDICS

Alerts, Notices, and Case Reports

Ingestion of Poison Hemlock (*Conium maculatum*)

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DESPITE ITS PROFOUND toxicity and wide distribution, poison hemlock (*Conium maculatum*) is an uncommon cause of poisoning in children. We report a case of poison hemlock ingestion.

Report of a Case

The patient, a healthy 4-year-old boy, and his father ingested the green tops of "wild carrots" growing in their backyard at about 3 PM on the day of admission. Within 30 minutes, the child became sleepy and took a nap. This was unusual for him. Two hours later, his father could not wake him up, and the patient had vomited green material in his bed. He was immediately taken to an emergency department. The child had no history of trauma, seizures, or fever. His father remained asymptomatic.

On physical examination, the patient's pulse rate was 100 beats per minute, and the respiratory rate was 26 per minute. His pupils were small and reactive, and the gaze was disconjugate. His neck was supple. The lungs, heart, and abdomen were unremarkable. There were no signs of trauma. On neurologic examination, there was semipurposeful response to noxious stimuli in the upper extremities and withdrawal in the lower extremities.

A complete blood count, electrolytes, blood urea nitrogen concentration, serum creatinine level, glucose level, prothrombin and partial thromboplastin times, and arterial blood gas values were within normal limits. A toxicology screen was negative. Radiographs of the chest and abdomen were normal.

Infusions of a dextrose solution and nalorphine hydrochloride produced no clinical improvement. The patient's stomach was lavaged, and he was given activated charcoal. During the first 90 minutes, he became progressively less responsive, but maintained an adequate gag reflex. Over the next hour, he began responding to simple commands, and within four hours he was awake and talking to his parents. He was discharged two days later with normal physical findings.

Figure 1.—The photograph shows the leaves and stalk of the hemlock plant (*Conium maculatum*).

A plant identified by the patient's father as identical to the others that both he and the patient ate was submitted to the Intermountain Herbarium, Logan, Utah, for taxonomic identification. Analysis by gas chromatography and mass spectrometry confirmed the presence of piperidine alkaloids characteristic of poison hemlock. The leaves contained 850 μg of γ-coniceine per gram of fresh plant.

Discussion

Conium maculatum is a poisonous biennial herb that grows erect to an average height of 1 to 3 m (3¼ to 9¾ ft).[1] The larger stems of maturing plants contain numerous purple spots that are an identifying characteristic. First-year-growth plants have fine, light-green, fernlike leaves (Figure 1) and usually grow no taller than 46 cm (18 in). Poison hemlock has a long white taproot that is solid and parsniplike. Plants generally persist in localized stands because the seeds drop near the parent plant. Occasionally seeds are spread by water, birds, or rodents.

Poison hemlock was introduced into the United States from Europe as an ornamental plant. It has become widespread and frequently grows in waste places, along roadsides, ditch banks, fence rows, and in uncultivated areas or anywhere adequate moisture is available. Its distribution is nationwide.

The toxins in poison hemlock are simple piperidine alkaloids. Coniine and γ-coniceine (Figure 2) are the predominant toxicants and not only have been implicated in overt toxicity in animals and humans but have been shown to induce congenital birth defects in livestock species.[2] The oral median lethal dose in mice for

(Frank BS, Michelson WB, Panter KE, Gardner DR: Ingestion of poison hemlock (*Conium maculatum*). West J Med 1995; 163:573-574)

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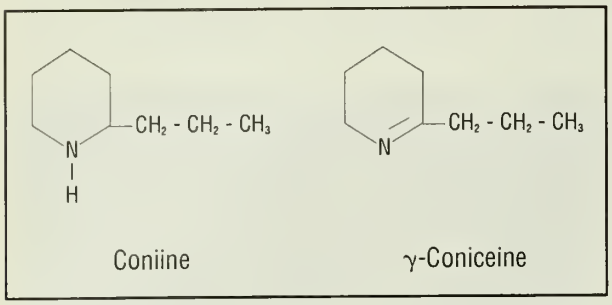

Figure 2.—The graphic formula of the alkaloids coniine and γ-coniceine, the predominant toxins of the hemlock plant, is shown.

γ-coniceine, the most toxic and most plentiful of the alkaloids, is 12 mg per kg.[3]

The mechanism of action of these alkaloids is twofold. The most serious effect occurs at the neuromuscular junction where they act as nondepolarizing blockers, similar to curare.[3] Death, when it occurs, is usually caused by respiratory failure. As a result of their action at the autonomic ganglia, the toxins produce biphasic nicotinic effects, including salivation, mydriasis, and tachycardia followed by bradycardia.[3] Less commonly, rhabdomyolysis and acute tubular necrosis have occurred.[4]

Poison hemlock is often confused with water hemlock (*Cicuta* species) because the two are similar in appearance and belong to the same family. The toxin in water hemlock, cicutoxin, has primarily central nervous system effects, including seizures.

Poison hemlock poisoning may be suspected in patients with an altered level of consciousness, myalgias, fasciculations, or flaccid paralysis following the ingestion of a plant substance. Supportive laboratory data include elevated muscle enzyme levels and myoglobinuria.[5] Elevated values on liver function tests have also been seen.[5] Routine plant toxin screens in biologic specimens are not commonly done except for those substances abused and for which drug screens are available. A method for a multiresidue chemical screen for alkaloids in plant material was recently described that provides the basis for confirming a case of poison hemlock or water hemlock toxicosis.[6]

Because no antidote exists for coniine poisoning, treatment is supportive.[7] Respiratory support and gastric decontamination should be instituted immediately. Anticonvulsants should be administered as needed. Forced diuresis may be useful in preventing renal failure from rhabdomyolysis and myoglobinuria.

The relatively short course and limited symptoms that our patient manifested can probably be explained by the small amount of plant ingested, the vomiting at home, and finally, the gastrointestinal decontamination that limited the quantity of toxin absorbed.

That ingestions of poison hemlock are not more common has been attributed to the plant's "mousy" odor, bitter taste, and burning of the mouth, throat, and abdomen on ingestion.[8] The father of this patient said that the plants tasted like "carrot tops."

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Multiple Organ Dysfunction Caused by Parvovirus B19

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HUMAN PARVOVIRUS B19 infection was first described in 1975. Erythema infectiosum (fifth disease) is the most commonly recognized parvovirus B19 infection in children. It has also been shown to be the primary etiologic agent of aplastic crisis in persons with chronic hemolytic anemia as well as being associated with cases of arthritis, purpura, and congenital infections manifesting as spontaneous abortion, stillbirth, or fetal hydrops.[1,2] We describe the case of a child with multiple organ dysfunction involving the skin, liver, heart, and hematopoietic system caused by parvovirus B19 infection, and we review published literature on B19-induced myocarditis and multiple organ dysfunction.

Report of a Case

The patient, a 19-month-old previously healthy female infant presented with an eight-day history of fever and a generalized erythematous macular rash that was first noted on the abdomen. Fifteen days before admission, she was admitted to a hospital with two generalized tonic-clonic seizures, bloody diarrhea, vomiting, and fever.

(Chundu KR, Lal S, Bartley DL: Multiple organ dysfunction caused by parvovirus B19. West J Med 1995; 163:574-576)

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ABBREVIATIONS USED IN TEXT

DIC = disseminated intravascular coagulation
Ig = immunoglobulin

Blood and cerebrospinal fluid cultures revealed no growth, and she was treated with phenobarbital and the combination drug, trimethoprim and sulfamethoxazole. Immunizations were current for age, including a measles, mumps, and rubella virus vaccine administered three weeks before admission.

The review of systems was notable for mild rhinorrhea, vomiting, diarrhea, and decreased urine output. Her temperature was 39°C (102°F) with a pulse of 175 beats per minute, respirations 28 per minute, and blood pressure 122/70 mm of mercury. The conjunctivae were clear. On oral examination she had cracked lips, diffuse erythema of the oropharynx, and a normal tongue. Shotty lymphadenopathy was noted in the right upper cervical area. A grade 2/6 ejection systolic murmur was heard at the left sternal border. The abdomen was soft, and no organomegaly was noted. She had nonpitting edema of the hands and feet. A morbilliform, pruritic rash was present over the entire body, sparing the body creases, palms, and soles, with no desquamation observed. The remainder of the physical examination findings were unremarkable.

Laboratory values were as follows: peripheral leukocyte count, 5.4×10^9 per liter (5,400 per mm^3), with 0.57 (57%) neutrophils, 0.09 (9%) band forms, 0.29 (29%) lymphocytes, 0.02 (2%) monocytes, and 0.03 (3%) eosinophils; a platelet count was 289×10^9 per liter (289,000 per mm^3). A reticulocyte count was not done at the time of admission. The hemoglobin level was 105 grams per liter (10.5 grams per dl), and the hematocrit was 0.32 (32%). Serum electrolytes and urinalysis were within normal limits. The 25-day hospital course is summarized by each system.

Infectious Disease

The patient remained intermittently febrile (39°C to 40°C [102°F to 104°F]) for the first two weeks of the hospital stay, with leukocyte counts ranging from 10 to 34 leukocytes $\times 10^9$ per liter (0.15 to 0.22 neutrophils, 0.05 to 0.09 band forms, 0.4 to 0.45 lymphocytes, and 0.1 to 0.21 eosinophils). The platelet count gradually fell to a low of 62×10^9 per liter on day 12 and recovered to normal levels by day 15 of her hospital stay. Serologic tests for rubella virus, measles virus, cytomegalovirus, herpes simplex virus, Epstein-Barr virus (viral capsid antigen immunoglobulin [Ig] G and IgM), hepatitis A virus (IgM), hepatitis B surface antigen and antibody, and *Mycoplasma* species (IgG and IgM) were all negative. Serologic testing for parvovirus B19 done on day 10 by enzyme immunoassay (MarDx Parvovirus B19 EIA Test kit, Cat# 40-9096G), revealed a parvovirus IgG of 2.29 and parvovirus IgM of 2.77 (>1.2 = "antibody detected"). The B19 IgM test was done after pretreatment of the serum to remove IgG. On day 3, the antistreptolysin O titer was slightly elevated (>200, <300 units), and when repeated on day 11, it was less than 200. Antinuclear and anti-DNA antibody tests were negative. Serum CH50, C3, and C4 levels were normal. A serum IgE level was elevated at 680 IU per ml (normal range, 0.1 to 370). The erythrocyte sedimentation rate was initially increased at 43 mm per hour but decreased to less than 25 mm per hour by the end of the first week and remained low thereafter. Several blood, urine, and stool cultures were negative. Viral cultures of specimens of nasopharynx and stool were negative. A throat culture was negative for β-hemolytic streptococci.

Ascites developed on the patient's seventh hospital day. Acid-fast stain and routine mycobacterial and fungal cultures of ascitic fluid were negative. A skin biopsy of the dermatitis done on day 9 showed interface dermatitis with vacuolar and psoriasiform changes, consistent with either a drug reaction or a viral infection.

Cardiovascular System

Echocardiography and an electrocardiogram were normal on day 3. On day 10 of the hospital course, signs of congestive heart failure developed, and an echocardiogram at that time revealed a dilated left atrium and ventricle and decreased left ventricular function with a shortening fraction of 17% (normal, 28% to 44%). Tricuspid and mitral regurgitation were also noted. Substantial abatement of the congestive heart failure was noted after a dobutamine hydrochloride drip at 12 μg per kg per minute was instituted. The patient showed improvement of left ventricular function by clinical examination and echocardiogram and was discharged home on a regimen of digoxin and captopril. An echocardiogram at the time of discharge showed substantial improvement of the cardiac function (shortening fraction of 30%).

Respiratory System

Bilateral pleural effusions associated with moderate respiratory distress developed on day 7, but the patient never required mechanical ventilation. Pleural effusions were thought to be due to hypoalbuminemia and congestive heart failure.

Gastrointestinal System

The patient's abdominal girth increased over the hospital course with both hepatosplenomegaly and ascites. Serum aminotransferase levels (aspartate and alanine) rose to a maximum of 370 and 311 U per liter, respectively, on day 5 and gradually decreased to normal values by day 14. The lactate dehydrogenase level peaked at 6,201 U per liter on day 11, and the isoenzyme pattern revealed elevated lactate dehydrogenase 3, 4, and 5 levels, consistent with pulmonary and hepatic dysfunction. Bilirubin and alkaline phosphatase levels were elevated to 50 μmol per liter (2.9 mg per dl) and 410 U per liter, respectively, on day 6 to 7 and decreased to normal values by day 16. The serum albumin value was decreased (20 to 30 grams per liter [2 to 3 grams per dl]) in the first two weeks of the hospital course.

Hematopoietic System

Disseminated intravascular coagulation (DIC) developed on day 5 of the patient's hospital course, characterized by a prolonged prothrombin time (>15 seconds) and partial thromboplastin time (>45 seconds), thrombocytopenia (platelet count, 65×10^9 per liter), and schistocytes on the peripheral blood smear. She received several transfusions of fresh frozen plasma, cryoprecipitate, and vitamin K with resolution of the DIC by day 14 of her hospital stay.

Two weeks into the hospital admission, her fever, liver and heart failure, and DIC started to resolve, and by three weeks the patient was afebrile and feeding well; she was discharged home on day 25.

Discussion

The most likely diagnosis in our patient is human parvovirus B19 infection with multiple organ dysfunction. The absence of leukocytoclastic vasculitis on the skin biopsy, a negative antinuclear antibody test, the absence of joint and renal involvement, and the evolution of the skin lesions argue against a drug-induced, serum sickness-like reaction. The clinical spectrum of parvovirus B19-associated diseases described in children includes erythema infectiosum, purpura, bronchiolitis, gastroenteritis, chronic anemia, arthralgia or arthritis, encephalitis, and mesenteric lymphadenitis.[3]

We reviewed the literature from 1976 through 1994 for reports of myocarditis or multiple organ dysfunction associated with parvovirus B19 infection in patients between the ages of 1 month and 18 years. Two cases of B19 myocarditis have been reported in children.[3,4] The first case occurred in a previously healthy 1-year-old male infant who presented to the hospital in congestive heart failure. The patient had facial erythema a few weeks before admission to the hospital. He responded well to digoxin and furosemide therapy initially. Two weeks into the hospital course, he had a relapse resistant to therapy and died of uncontrollable heart failure.[4] Parvovirus B19 structural proteins were detected by an immunocytochemical technique in the myocardial tissue sections on necropsy and IgM antibodies against the B19 in the serum.

The second case was of a 5-month-old female infant who presented with fever, tachycardia, hepatomegaly, mitral insufficiency, and congestive heart failure.[3] Echocardiography revealed a dilated and hypokinetic left ventricle, and therapy with digoxin and diuretics was instituted. A year after therapy, the patient still showed clinical and echocardiographic signs of heart failure, and heart transplantation was being considered. The diagnosis was established by a positive-capture immunoassay for IgM antibodies against the parvovirus B19. The diagnosis of myocarditis was supported by clinical and echocardiographic findings in all three cases.

There are no previous reports of B19 infection-induced hepatitis or multiple organ dysfunction in older children. Our patient had serologic evidence of recent B19 infection and evidence of liver, heart, skin, and hematopoietic system dysfunction. This case and the two previously reported cases of myocarditis provide important information regarding the expanding spectrum of clinical disease attributed to B19 infection. Although both of the previously reported cases of myocarditis had adverse outcomes, our patient had a good outcome, with complete resolution of the congestive heart failure and normal ventricular function by echocardiogram at three-months' follow-up.

Previous reports of intrauterine B19 infection have documented cardiac insufficiency that was thought due to hypoplastic anemia-induced high-output cardiac failure[5] or direct infection of the myocardium.[6] Our patient had substantial liver involvement indicated by hyperbilirubinemia, elevated aminotransferase levels, and prolonged prothrombin and partial thromboplastin times. It is of interest that the child was only slightly anemic despite having a severe B19 infection, similar to the case reported in the literature.[4] Our patient had no history or laboratory evidence to suggest immune deficiency as the cause of this severe B19 infection that affected multiple organs. Experiences from these cases suggests that parvovirus B19 infection should be considered in the differential diagnosis of ill children with myocarditis and multiple organ system dysfunction.

Clinical and laboratory evidence is accruing to suggest that parvovirus B19 has a wider tropism than just erythroid progenitor cells. It has been shown to bind to blood group P antigen, and the tissue distribution of this antigen—erythroid cells, endothelium, and cardiac myocytes—might explain the tropism to these tissues.[7] Another explanation for the multiorgan involvement can be immune responses to the infection rather than active infection in other tissues. Improved quality and availability of the diagnostic tests and higher clinical suspicion will likely broaden the clinical spectrum of disease and lead to a better understanding of the pathophysiology of parvovirus B19 infection.

Acknowledgment

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Hypocalcemia Due to Avid Calcium Uptake by Osteoblastic Metastases of Prostate Cancer

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A THIRD OF PATIENTS WITH prostate cancer and bone metastases have a low serum calcium concentration,[1-3] and some have severe hypocalcemia. One mechanism, avid calcium uptake by osteoblastic bone metastases, was postulated more than 30 years ago.[4] When we reviewed the literature, however, we could not find any cases we thought were adequately documented.

Herein we describe the case of a patient with hypocalcemia and prostate cancer with diffuse osteoblastic metastatic involvement of the entire rib cage and spine. Clinical investigation provided for the first time overwhelming evidence that hypocalcemia was caused by avid calcium uptake by the osteoblastic metastases.

Report of a Case

The patient, an 82-year-old man with an indwelling Foley catheter, lived in a nursing home because of dementia. In December 1992, he was sent to Meridia Huron Hospital (Cleveland, Ohio) because of decreasing appetite, increasing lethargy, fever, and mild shortness of breath of a few days' duration. His temperature was 38°C, blood pressure 146/96 mm of mercury, heart rate 92 beats per minute, and respiratory rate 28 per minute. He was disoriented, lethargic, and cachectic. The lungs on examination were unremarkable. There was a 1-cm decubitus ulcer on the buttock. A firm nodule was felt in the right lobe of the prostate.

On admission, the following laboratory test values were elicited: serum calcium, 1.67 mmol per liter (6.7 mg per dl); phosphorus, 1.07 mmol per liter (3.3 mg per dl); alkaline phosphatase, 1,023 U per liter (normal, 37 to 107); albumin, 27 grams per liter; total protein, 59 grams per liter; urea nitrogen, 12.1 mmol per liter (34 mg per dl); creatinine, 110 μmol per liter (1.2 mg per dl); and magnesium, 0.95 mmol per liter (normal, 0.66 to 0.99). A serum sodium level was 152, potassium 4.6, bicarbonate 25, and chloride 113 mmol per liter. A serum glucose level was 7.7 mmol per liter (139 mg per dl), and an aspartate aminotransferase level was 44 U per liter (normal, 12 to 45). His hemoglobin level was 70 grams per liter; mean corpuscular volume, 89 fl; leukocyte count, 8.1×10^9 per liter; and platelet count, 261×10^9 per liter. Proteinuria (1.0 gram per liter) and moderate hematuria were found on urinalysis, and the urine sediment contained 11 to 25 leukocytes and many bacteria per high-power field, although nitrite and leukocyte esterase were not detected. The initial evaluation suggested dehydration and urinary tract infection, and a regimen of intravenous fluids and antibiotics was started.

Studies were done to identify the cause of hypocalcemia and the extremely elevated alkaline phosphatase level. An acid phosphatase level was 68 U per liter (normal, 0 to 5.7); prostate-specific antigen, 665 μg per liter (normal, 0 to 4.0); ionized calcium, 0.90 mmol per liter (3.6 mg per dl; normal, 1.15 to 1.35 mmol per liter; performed by the Nichols Institute [San Juan Capistrano, California], ion-specific electrode); urinary calcium, 0.3 mmol (12 mg) per 24 hours; intact (immunoradiometric assay) parathyroid hormone, 95 ng per liter (performed by the Nichols Institute; normal, 10 to 65 ng per liter), when the serum calcium level was 1.6 mmol per liter (6.5 mg per dl); serum 25-hydroxyvitamin D, 180 nmol per liter (normal, 22 to 130); and 1,25-dihydroxyvitamin D, 247 pmol per liter (normal, 36 to 144). Other studies included a serum vitamin B_{12} level, 630 pmol per liter (normal, 180 to 920); folic acid, 58 nmol per liter (normal, 6 to 49); and ferritin, 1,760 μg per liter (normal, 30 to 300). X-ray films showed a striking diffuse increase in opacity of the entire rib cage and spine since previous x-ray films, consistent with an osteoblastic process. A prostatic biopsy showed moderately differentiated adenocarcinoma.

The patient died two weeks after admission. Postmortem random needle biopsies of rib and iliac crest confirmed the presence of diffuse metastatic adenocarcinoma. The presence of many osteoblasts and increased trabecular matrix were consistent with new bone formation.

Discussion

A low serum total calcium concentration has been reported in 14% of all patients with carcinoma of the prostate and in 23% to 32% of those with bone metastases.[1-3] Usually this is due to hypoalbuminemia; true hypocalcemia, defined as a low ionized calcium concentration, is much less common, occurring in about 2% of all cases of prostate cancer.[3] Even so, prostate cancer is a common disease; 165,000 new cases were expected in the United States in 1993.[5] Thus, we should expect about 3,300 patients per year to have true hypocalcemia and a much larger number to have a low total calcium concentration. In view of these estimates, we were surprised to find a paucity of articles dealing with the pathogenesis of hypocalcemia in patients with prostatic cancer.

(Szentirmai M, Constantinou C, Rainey JM, Loewenstein JE: Hypocalcemia due to avid calcium uptake by osteoblastic metastases of prostate cancer. West J Med 1995; 163:577-578)

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True hypocalcemia can develop in various ways. Because many of these patients are old and have other medical problems, causes of hypocalcemia unrelated to prostate cancer itself must be considered. The most common of these is renal failure, and others include hypomagnesemia and malabsorption.

There are several ways in which hypocalcemia might be due directly to prostate cancer metastatic to bone. One mechanism might be impaired 1α-hydroxylation, leading to low levels of 1,25-dihydroxyvitamin D. This has been well documented in certain connective tissue tumors[6] and in two cases of prostate cancer.[7]

Avid uptake of calcium by osteoblastic metastases of prostate cancer was postulated as a cause of hypocalcemia in three patients whose cases were reported individually.[3,8,9] Such patients would be expected to have secondary hyperparathyroidism and, as a consequence, a low or low-normal serum phosphorus level and an elevated or high-normal serum 1,25-dihydroxyvitamin D concentration. Furthermore, the absence of other possible causes of hypocalcemia would make avid uptake by osteoblastic metastases more likely as the sole cause of hypocalcemia. Unfortunately, none of the patients in the cases previously reported met all these conditions.

The serum parathyroid hormone level was slightly elevated in one reported case,[8] but the high serum phosphorus and low 1,25-dihydroxyvitamin D concentrations suggest resistance to parathormone. Another patient had an increased serum parathormone concentration, but the 1,25-dihydroxyvitamin D concentration was not measured,[9] and the serum 25-hydroxyvitamin D level was at the lower limit of normal. The third patient had a normal serum parathormone concentration despite mild chronic renal insufficiency, possibly because of hypomagnesemia, and a serum 1,25-dihydroxyvitamin D level was near the lower limit of normal.[3] In fact, calcium malabsorption due to vitamin D deficiency, relatively low levels of 1,25-dihydroxyvitamin D, or both, probably played a role in all three of these patients.

In our patient, both total and ionized serum calcium levels were low, documenting true hypocalcemia. The serum magnesium concentration was well within normal limits. Clinically important renal insufficiency was not present; the serum creatinine level was only marginally elevated, and there was no phosphorus retention. Hypercalciuria was excluded.

Our patient's elevated parathormone and 1,25-dihydroxyvitamin D concentrations indicated a normally functioning regulatory mechanism, although higher values might have been expected for this degree of hypocalcemia. Because we thought one of the previously reported patients might have had peripheral resistance to parathormone,[8] we considered this possibility in our patient; the low-normal serum phosphorus and elevated 1,25-dihydroxyvitamin D levels provided good evidence against this. We did not measure the urinary phosphorus excretion, so we cannot exclude some blunting of the phosphaturic response to parathormone.

The normal vitamin B_{12} and folate concentrations and the high serum ferritin level provide evidence against generalized malabsorption. The elevated concentration of 1,25-dihydroxyvitamin D provides evidence against calcium malabsorption or tumor-related impairment of 1α-hydroxylation. Furthermore, calcium malabsorption could not explain the generalized increase in bone opacity seen on x-ray films.

In summary, this case provides convincing evidence that avid uptake of calcium by osteoblastic metastases can cause true hypocalcemia in patients with prostatic cancer.

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Topics in Primary Care Medicine

Osteoarthritis
A Continuing Challenge

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Osteoarthritis is a disorder of cartilage that affects almost 85% of the population by age 75. A lack of rigorous clinical and radiographic criteria for defining the disorder makes precise determination of its prevalence impossible. The process of wear and tear explains many manifestations of osteoarthritis, but it does not account for some of the clinical findings or the biochemical changes in osteoarthritic cartilage. Thus, other factors such as heredity, hormones, and diet may play a role. Treatment consists of teaching patients about their disease, alleviating pain, and preserving joint function. Nonsteroidal anti-inflammatory drugs may be no more effective than simple analgesics in relieving the pain of this disorder. Moreover, some nonsteroidal anti-inflammatory drugs can adversely affect cartilage metabolism, and most are possibly dangerous in elderly patients. Drugs that inhibit the production or activity of chondrolytic enzymes can slow the degeneration of cartilage in some animals, but their effects on humans with osteoarthritis are unproved. The surgical repair of severely damaged joints can have gratifying results.

(Sack KE: Osteoarthritis—A continuing challenge. West J Med 1995; 163:579-586)

Osteoarthritis is in many ways like the weather—ubiquitous, often unnoticed, sometimes dramatic in its effects, and largely unexplained. To carry the analogy further, everyone talks about osteoarthritis, but nobody seems to be doing much about it.

The name may be a misnomer. The disorder's primary cause is not likely to reside in bone,[1,2] and inflammation is not prominent in its initial stages.[3] Nevertheless, the term osteoarthritis serves its purpose—it is short, physicians and patients know what it means, and it has a more benign connotation for patients than does "degenerative joint disease."

The prevalence of osteoarthritis in the population is hard to determine because the disorder cannot be defined precisely. Do all patients with joint pain and radiographic evidence of osteophytes have osteoarthritis?[4,5] Does a normal radiograph exclude its diagnosis in a patient with joint pain?[6] Can osteoarthritis be completely asymptomatic?[7] Are osteophytes a normal consequence of aging?[4] Will our ability to quantify cartilaginous loss with magnetic resonance imaging scans alleviate or enhance our confusion?[8]

Osteoarthritis rarely occurs before age 40, but by age 75, at least 85% of the population have either clinical or radiographic evidence of the disease.[9] Although it occurs more frequently and tends to affect more joints in women, for those younger than 45, it affects both sexes equally.[10] White populations from developed countries have similar rates of osteoarthritis in the hands and the knees.[10] By contrast, black American women have more osteoarthritis of the knees.[11] Although it is relatively uncommon (less than 5%) in the hips in Chinese[12] and in most black populations,[13] its prevalence in many European communities approaches 25%.[13]

What Causes Osteoarthritis?

For many years, investigators have embraced the concept that osteoarthritis is a disease of wear and tear. Some of its clinical manifestations do not fit this notion, however. For instance, why do women have a propensity for prominent bony enlargement of the distal interphalangeal (Heberden's nodes) and proximal interphalangeal (Bouchard's nodes) joints,[14] whereas men who do manual labor show no such predisposition for the disease in their hands?[15,16] Why does an inflammatory form of osteoarthritis tend to affect women near menopause?[17-19] And why is cartilage in patients with the disorder biochemically different from cartilage in older people without it?[20]

Understanding the structure and function of normal cartilage may provide some clues to the pathogenesis of osteoarthritis. Articular cartilage provides a low-friction bony interface greatly capable of absorbing shock. These functions are dependent on the composition of the cartilage matrix, which consists of collagen fibers (which make up 50% of the dry weight of cartilage) intermingled with proteoglycans—high-molecular-weight aggregates of glycosaminoglycans (mucopolysaccharides) bound to protein chains (Figure 1).[20-22] From a functional standpoint, collagen gives cartilage tensile strength and allows it to resist shear forces occurring during motion under

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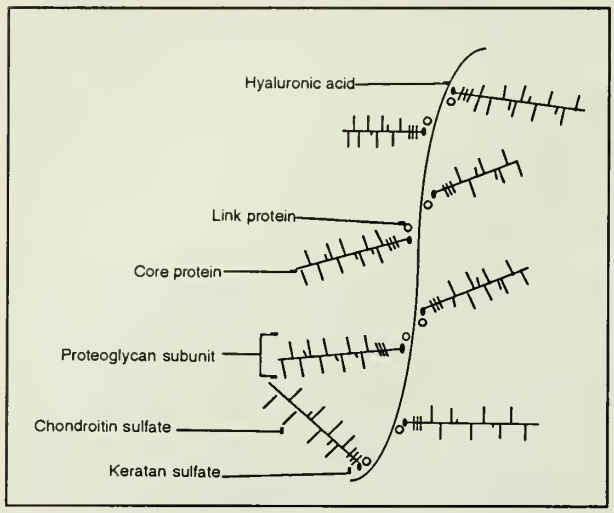

Figure 1.—A schematic representation of a proteoglycan aggregate is shown.

load. Collagen also constrains the negatively charged hydrated proteoglycans. This produces a large swelling pressure and gives cartilage its elasticity and resistance to compression.[21] Under high-load conditions, proteoglycans release water and provide lubrication at the cartilage surface (hydrostatic lubrication).[20,21] Not surprisingly, areas of cartilage that are subjected to heavy loads contain greater concentrations of proteoglycans.[23,24]

Damage to the collagen fibers or to the proteoglycan matrix of cartilage causes a loss of its normal lubricating and shock-absorbing functions. Unfortunately, cartilage responds poorly to injury because of a limited blood supply and the lack of undifferentiated mesenchymal cells capable of initiating healing. Thus, repair tends to be spotty, and instead of containing collagen found in normal articular cartilage, the newly formed cartilage contains collagen characteristic of fibrocartilage.[25]

The cartilage in patients with osteoarthritis is not simply "old and worn out" (Table 1). Compared with normal cartilage, aging cartilage contains less water, a higher ratio of keratan to chondroitin sulfate, and fragmented link protein. Yet, there is no evidence that aging cartilage is biochemically inferior to normal cartilage. Cartilage in patients with osteoarthritis, on the other hand, contains more water, less keratan sulfate than in normal cartilage, and normal link protein.[20] Structural changes in the proteoglycan macromolecules are key features of osteoarthritis and, together with ultrastructural changes in collagen fibers, cause deterioration in the function of cartilage. The chondrocyte, previously thought to be an inert cell, is likely an important participant in this process. It has anabolic or catabolic functions, depending on local events. In contrast to rheumatoid arthritis where the synovium is the primary source of proteolytic enzymes, in osteoarthritis the chondrocyte seems to be the principal producer of these substances.[26,27] Table 2 contains a partial list of cytokines likely to be important in the pathogenesis of osteoarthritis.[27,28]

TABLE 1.—*Composition of Aging Cartilage Versus That Affected by Osteoarthritis**

Chemical Composition	*Aging Cartilage*	*Osteoarthritic Cartilage*
H_2O	↓	↑
Glycosaminoglycans	Normal or slightly ↓	↓
Keratan sulfate	↑	↓
Chondroitin sulfate	↓	Early ↑, then ↓
Hyaluronic acid	↑	↓
Proteoglycans	†	‡
Link protein	Fragmented	Normal

↓ = amount decreased, ↑ = amount increased

*Modified from Brandt and Fife.[20]
†Decreased extractability and normal aggregation.
‡Increased extractability and decreased aggregation.

TABLE 2.—*Cytokines in Osteoarthritis*

Cytokine	*Effect*
Interleukin (IL) 1	Stimulates loss of proteoglycan (PG) from cartilage, release of proteases, synthesis of IL-6 and type I collagen Inhibits cell division in chondrocytes, synthesis of type II collagen
Interferon gamma	Suppresses synthesis of type II collagen
Tumor necrosis factor alpha	Stimulates synthesis of proteases
IL-6	Inhibits IL-1–induced breakdown of cartilage and synthesis of cartilage PG Stimulates production of tissue inhibitor of metalloproteases (TIMP)
Transforming growth factor beta	Stimulates synthesis of collagen and TIMP Inhibits synthesis of collagenase
Insulin-like growth factor I	A potent anabolic factor of cartilage

Role of Trauma

Could trauma initiate these biochemical events? Although loading and motion are important in preserving normal cartilage metabolism and function,[29-33] exerting excessive force on cartilage can have the opposite effect.[34-36] Thus, activities such as jumping or twisting can damage articular cartilage, and an injury that results in an unstable joint or that damages the normal cushioning structures, such as a meniscus in the knee, can render cartilage vulnerable to stress. It has been suggested that trauma to cartilage can be more subtle. Indeed, a subset of the normal population habitually loads their legs at heel strike and thus may be predisposing themselves to joint damage.[35] Having abnormally dense bone could also predispose cartilage to injury,[37-41] but this idea has been disputed.[42-44] Finally, an intact neuromuscular system is important in maintaining normal joint function. Although deficits in sensory nerves are not an important cause of osteoarthritis, abnormalities in the muscular reflex that

normally protects the joints could increase its severity.[45]

In 1971 a mechanism was proposed for the occurrence of "nodal" osteoarthritis in women.[15] It was postulated that the smaller surface area of the distal joints of the fingers subjects these joints to greater pressures per square inch than the more proximal joints. Furthermore, fine motor activity uses the deep flexor tendons that insert into the distal phalanges, but these tendons are "splinted" by the superficial tendons during power-grip activities. Thus, knitting and sewing would likely produce more node formation than hammering and sawing. It was subsequently shown that in an industrial setting, node formation in the fingers correlated more with repetitive, fine motor activity than with gender.[16]

Role of Heredity

Early studies suggested that generalized osteoarthritis, which typically affects the hands, knees, and spine, occurs in two forms—one in association with Heberden's nodes, the other without such nodes.[46-48] Nodal osteoarthritis showed an inheritance pattern consistent with an autosomal gene, dominant in females and recessive in males.[49,50] Non-nodal osteoarthritis showed a polygenic inheritance.[51] Lacking in these studies, however, is information regarding occupation and other physical activities involving the hands. Current research has linked abnormalities in the type II procollagen gene *COL2A1* on chromosome 12 with some familial forms of generalized erosive osteoarthritis.[52,53] Patients with these abnormalities typically have an associated chondrodystrophy, however. Such genetic defects do not account for most cases of osteoarthritis.[54]

Role of Estrogen

The predisposition of women to severe osteoarthritis and the tendency for the inflammatory form to occur near menopause suggest that estrogens play a role in this disorder.[55] Indeed, the articular cartilage of some animals contains estrogen receptors.[56-58] Whether estrogens alleviate or worsen the disease in animals seems to depend on the model being studied.[59,60] Possibly detrimental effects of estrogens on cartilage include suppressing chondrocyte proliferation, suppressing proteoglycan synthesis, and stimulating cytokine release from macrophages and chondrocytes.[61]

Role of Diet

How might diet affect the development or severity of osteoarthritis? Certainly obesity plays a role in the occurrence and progression of the disease in the knees.[62-66] This could be ascribed to the mechanical effect of increased weight, but it is hard to understand why obesity is a modest predictor of osteoarthritis in the distal interphalangeal and first carpometacarpal joints.[67] In some animal models, a diet high in saturated fat increases the severity of the disease,[68-70] but in other studies this effect has been hard to reproduce.[71] Some secondary forms of osteoarthritis have a presumed dietary association.[72] Kashin-Beck disease, for example, is a noninflammatory disorder of enchondral bone growth endemic to eastern Siberia, northern China, and northern Korea. Dystrophic changes in the epiphyseal and metaphyseal areas lead to secondary degenerative changes in peripheral joints and the spine. Proposed causes have included infectious agents and excesses or deficiencies of trace elements.[72-74]

Clinical Aspects of Osteoarthritis

Osteoarthritis affects most movable joints. Pain in a joint with movement along with articular bony enlargement are typical manifestations of, but are not specific for, the disease. Nevertheless, certain aspects of joint involvement are fairly consistent and deserve mention.

In the hands, osteoarthritis affects primarily the distal interphalangeal, proximal interphalangeal, and first carpometacarpal joints (Figure 2). Deformity or a decrease in motion of the joint occurs gradually, and deviation tends to be in a lateral direction, unlike the vertical deformity of rheumatoid arthritis. Metacarpophalangeal involvement is distinctly unusual, but elderly patients with extensive osteoarthritis of the hands occasionally have mild swelling or subluxation of the metacarpophalangeal joints. Heavy manual labor also may cause degenerative changes in these joints.[75]

The wrists are virtually never involved, and if they are, this should suggest another diagnosis such as rheumatoid arthritis or pseudogout. Involvement of the first carpometacarpal joint, however, may give the wrist a "squared-off" appearance (see Figure 2).

Although osteoarthritis rarely affects the elbows in the absence of a metabolic disease or previous trauma, a subset of patients may have involvement of the elbows. These patients typically are men who have osteoarthritis in other joints, particularly the metacarpophalangeal joints.[76]

Osteoarthritis frequently affects the acromioclavicular joint. By contrast, the glenohumeral joint is not a common target. When degenerative changes occur in this joint, patients are likely to have a severe tear in the rotator cuff, allowing superior migration of the humeral

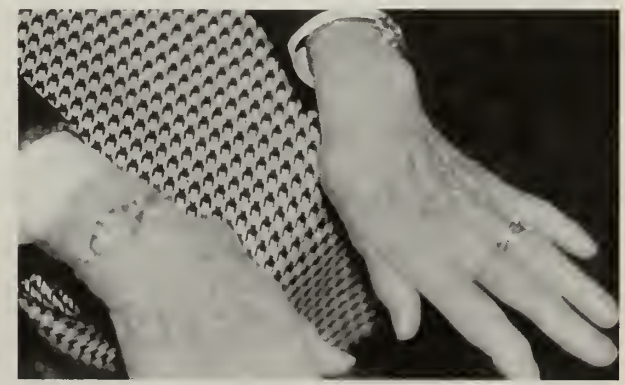

Figure 2.—Bony enlargement is seen of the distal interphalangeal joint of the index finger (Heberden's node) of a patient with osteoarthritis of the hand. The prominent first carpometacarpal joint gives the hand a squared-off appearance.

head.[77] Elderly women are susceptible to a destructive arthropathy of the shoulder ("Milwaukee shoulder"), presumably mediated by apatite crystals.[78]

Movable portions of the spine are susceptible to degenerative changes. The central gelatinous portion of the intervertebral disc (nucleus pulposus) gradually disappears with aging and is essentially nonexistent after age 45.[79] Thus, "degeneration" of discs is a normal phenomenon of aging. In the lower five cervical vertebrae, such changes could place abnormal stress on the posterior (zygoapophyseal) vertebral articulations, resulting in joint-space narrowing, subarticular sclerosis, and osteophyte formation—the hallmarks of osteoarthritis. Because the cervical spine is reputed to move about 600 times in an hour (whether awake or asleep), it is no wonder that at any given time about 10% of the population has a pain in the neck.[80] Although radiographs of the cervical spine typically show bony abnormalities of the facet joints and the posterolateral uncinate processes, caution must be used in ascribing pain in the neck or radicular symptoms to such changes.[81]

Osteoarthritis affects the hips (often both) more commonly in men than in women.[82] Heavy lifting might increase the risk of disease in this joint.[83] Other possible risk factors include leg-length discrepancy (the long leg will be affected), acetabular dysplasia, a slipped femoral epiphysis, and Legg-Calvé-Perthes disease. Most of the time, however, the cause is not apparent.[84] Pain from osteoarthritis in the hips typically occurs in the groin or anterior thigh, but occasionally in the buttock or even in the knees. Range of motion in the hip, particularly internal rotation, becomes limited. Weakness in the hip abductor muscles makes it difficult to keep the pelvis level during walking and causes a patient to tilt toward the affected side to swing the opposite leg forward (Trendelenburg gait).

The prevalence of osteoarthritis in the knees rises with age.[65,82,85] Although a third of people older than 65 have radiographic findings in the knee consistent with the disease, only 10% of this age group has pain in the knees and an abnormality of cartilage by visual or radiographic examination.[65,85] Obesity correlates strongly with osteoarthritis of the knees, particularly in women and in patients with disease of both knees.[64] Obese patients and those with a previous meniscectomy have more involvement of the tibiofemoral than the patellofemoral compartment.[66] Isolated patellofemoral disease is more common in young adults, either as a result of trauma or, in women, from recurrent patellar subluxation.[86] Although habitual physical activity of many types, including running, does not predispose to disease in the knees,[87,88] prolonged or repeated kneeling and squatting appear to be risk factors.[36] Characteristic physical findings include pain or crepitance on joint motion, tenderness along the tibiofemoral or patellofemoral articulations, and genu valgum (knock-knee) or genu varum (bowleg) deformity.

In the absence of repetitive trauma or chronic ligamentous injury, osteoarthritis seldom affects the ankles.[82,87,89] The first metatarsophalangeal joint, however, is a common target. Inflammation of the bursa overlying the medial aspect of this joint may produce a characteristic swelling (bunion).

TABLE 3.—*Other Conditions Causing Degeneration of Cartilage**

Cause	*Condition*
Inflammatory diseases	Rheumatoid arthritis Infection
Physical factors	Trauma—physical injury, obesity, mechanical derangement, neuropathic joint Ischemic necrosis of bone
Endocrine diseases	Diabetes mellitus Acromegaly
Metabolic diseases	Hemochromatosis Wilson's disease Ochronosis Crystalline—urate, calcium pyrophosphate, hydroxyapatite arthropathy
Nutritional (?)	Kashin-Beck disease Steroid injections (?)

*Modified from Sack.[97]

Looking at the pattern of osteoarthritis, the impression is that humans may have evolved faster than their joints could adapt.[90,91] After all, we developed an opposable thumb, assumed an upright posture, and learned to live well beyond our reproductive years. And we cannot regenerate new limbs.

Variations of Osteoarthritis

A "nodal generalized" form of osteoarthritis affects principally the distal and proximal interphalangeal and first carpometacarpal joints of the hands, but it also involves the hips, knees, metatarsophalangeal joints, and the spinal articulations.[46,48] Joint inflammation and exaggerated osteophyte formation can occur. An "erosive" type of osteoarthritis shows many features of generalized disease, but joint inflammation and subchondral erosive changes are more pronounced.[92-94] Patients with this form of the disease are typically women who have recently entered menopause.[55,95] The female predilection for nodal generalized osteoarthritis and the reported association of this disorder with the HLA-A1, B8 tissue type, Sjögren's syndrome, and thyroid disease suggest that this is an autoimmune disorder.[96]

When osteoarthritis occurs at atypical sites or is unusually severe, other factors may be operative (Table 3).[97] As a rule, any physical, inflammatory, or metabolic insult can predispose cartilage to further degenerative change. Particularly noteworthy is the occurrence of severe osteoarthritis in association with the deposition of calcium pyrophosphate dihydrate or apatite crystals.[98,99]

Laboratory Evaluation

Osteoarthritis causes few, if any, abnormal laboratory values. The erythrocyte sedimentation rate is typically normal but may show a modest increase in patients with

inflammatory osteoarthritis. Tests for rheumatoid factor or antinuclear antibodies are often positive in normal aging persons and therefore have little meaning when the clinical findings suggest only osteoarthritis. Synovial fluid obtained from joints affected by the disease typically shows normal viscosity and few leukocytes ($<2 \times 10^9$ per liter [2,000 per mm^3]) with a normal differential count (<0.3 [30%] polymorphonuclear cells). In rare cases, fluid from joints that have severe degeneration of cartilage or an associated deposition of crystals (such as calcium pyrophosphate dihydrate or apatite) will show a higher leukocyte count.

Radiographs in patients with osteoarthritis may show narrowing of the joint space, a marginal overgrowth of bone (osteophytes), subchondral bony sclerosis or cyst formation, or malalignment of the joint. Although these findings frequently constitute criteria for the diagnosis, they do not always correlate with clinical symptoms or with the condition of articular cartilage on arthroscopy.[100,101] Some radiographic changes, however, have prognostic importance. Thus, in hips, supralateral migration of the femoral head may carry a worse prognosis than medial migration.[102] Magnetic resonance imaging may show degenerative changes in cartilage when the plain radiograph does not.[103] Such studies are costly, however, and are useful only when planning surgical intervention.

Treatment

Grandma Moses treated her arthritis with sweet milk and turpentine.[104] The question is, can we do any better now? If the goal is to repair damaged cartilage, the answer is clearly no. If, however, the goal is to teach patients about their disease, alleviate pain, preserve joint function, or ultimately repair a severely damaged joint, then the answer is yes.

We can now provide patients a clearer picture of their long-term prognosis. For instance, studies show that osteoarthritis seldom impairs function of the hand, even if some pain and stiffness persist.[105,106] Furthermore, pain in the knees or hips may diminish as patients reach their mid-60s, even if damage to these joints is substantial.[107,108] And never underestimate the power of reassurance. In one study, patients who had monthly phone calls from lay personnel to discuss self-care issues had a substantial reduction of joint pain.[109]

Physical modalities provide the cornerstone for managing osteoarthritis. Activities that involve normal loading of joints are important in maintaining healthy cartilage.[29-33] A knowledgeable physical or occupational therapist can teach patients how to exercise safely and how to protect their joints while doing routine activities of daily living. For patients with disease of the hips, the simple measure of splitting heavy loads and carrying them in each hand, or carrying the load ipsilateral to the affected hip, will minimize the force exerted on that joint.[110] In osteoarthritis of the knees, weakness of the quadriceps muscle[111] and obesity correlate with symptoms.[62-67] Thus, sensible treatment would include muscle strengthening[112] and weight reduction.[113] Modifying shoes will occasionally improve the mechanics in knees[114] and relieve pain. Although it is hard to prove that physical modalities alter the course of osteoarthritis, such intervention may at least lessen symptoms. Two recent articles review the principles of exercise for patients with osteoarthritis.[30,115]

The cause of pain in this disease is conjectural.[116,117] Cartilage contains no nerve fibers, and synovitis does not always correlate with symptoms. Thus, it is no surprise that NSAIDs may be no better than simple analgesics like acetaminophen at relieving the pain of osteoarthritis.[118-121] Some NSAIDs adversely affect proteoglycan metabolism and could theoretically inhibit repair mechanisms in cartilage, but the effect of any particular NSAID on the eventual outcome of osteoarthritis is unknown.[122-127] Because these drugs are relatively toxic to elderly patients—the population at risk for having osteoarthritis—it is prudent to use them in their lowest effective dosage and only if they relieve symptoms more than simple analgesics.

Administering steroids intra-articularly can reduce pain in joints affected by arthritis.[128] This would indicate that inflammation has a role in this process, but placebo responses could also account for some of the "successes" of intra-articular steroid use in this disorder. Intra-articularly or parenterally administered steroids could affect chondrocyte metabolism and the production of cytokines and proteolytic enzymes, but studies of the effects of such treatment on experimental osteoarthritis give conflicting results.[129-138] Conceivably intra-articular steroid use could hasten the progression of the disease, but at least one study indicates that it takes less steroid to suppress chondrocyte protease synthesis than to suppress proteoglycan synthesis.[138]

Chloroquine and doxycycline can inhibit the production or activity of chondrolytic enzymes.[139] Calcitonin has anabolic effects in chondrocytes and can stimulate cartilage growth.[25] Although these substances have shown some promise in experimental models, it remains to be seen whether they will benefit patients with established osteoarthritis. Unfortunately, the positive results from the intra-articular administration of a chondroprotective agent such as hyaluronan[141-143] could not be duplicated in a recent controlled trial.[144] Applied topically, capsaicin, which depletes local sensory nerve terminals of substance P, can reduce pain and tenderness in small joints affected by osteoarthritis.[145,146] The long-term effects of such therapy are unknown.

Most patients with osteoarthritis will never need surgical treatment of their joints, but when pain is unrelenting or when joint function is severely compromised, such treatment can provide substantial benefit. The most gratifying results have come from remodeling or replacing a hip or knee. Surgical therapy is rarely necessary for osteoarthritis of the hand, but occasionally a patient may benefit from fusing, resecting, or replacing a joint. Similar procedures are helpful when the disease causes severe pain or deformity in the feet.

Arthroscopic debridement—trimming meniscal fragments, removing loose debris, shaving shaggy articular surfaces—may relieve symptoms in some patients with

disease of the knee. Abrading the articular surface does not offer any additional benefit.[147] Some investigators advocate lavaging the knee by means of an arthroscope or cannula in an attempt to remove phlogistic debris.[148] The long-term results of such treatment are unknown.

The Challenge

To meet the challenge of this disease, we must clarify the factors leading to its onset and progression and devise safe and practical methods of preserving cartilage and relieving pain. The recent report that cultured autologous chondrocytes can be used to repair deep cartilage defects is a step in the right direction.[149]

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Editorials

Modern Syphilis—Still a Shadow on the Land

In the early part of this century, 10% of the population of the United States and Europe was infected with syphilis. It touched all social strata and ages, from neonates to the elderly. Every physician was familiar with the disease in its many manifestations, and syphilis was so common that departments of dermatology and syphilology existed in many medical schools. Today, syphilis is a historical disease in the minds of much of the medical community, the policy makers, and the public, despite the fact that the incidence of infectious syphilis has been increasing since the mid-1950s, with discrete epidemics occurring at ten-year intervals. Why should we now be discussing this infection, as Judy L. Flores, MD, does with great thoroughness elsewhere in this issue of the journal?[1] Syphilis has not been featured on the covers of national news magazines. No celebrities have embraced it as their "pet" cause. No penicillin-resistant strains have been identified, and the dramatic late manifestations are increasingly rare. Yet, this disease persists, both in untreated individuals and in our society. In contrast to Lyme disease and the chronic fatigue syndrome, the lack of a public outcry about syphilis has resulted in only modest sums being committed to syphilis research and control, despite the fact that many more of our citizens are affected by syphilis than by these other conditions.

We have much to learn about, and from, syphilis: lessons in biology and medicine, and lessons in commitment and public policy. Syphilis is a fascinating and complex disease. It is caused by *Treponema pallidum*, a bacterium so fragile that it can be kept alive in the laboratory for only a few hours, yet so aggressive that it invades virtually every organ system, and so clever that some treponemes can persist in a host for decades despite the onslaught of an immune response powerful enough to spontaneously clear billions of their kin from the early skin lesions.

The two most recent epidemics of syphilis have occurred in patients who are at high risk for infection with the human immunodeficiency virus (HIV), homosexual men and African Americans. These epidemics have taught us much about the pathogenesis of syphilis and the interactions of these two sexually transmitted infections. Syphilis and other genital ulcer diseases are cofactors in the acquisition and transmission of HIV, probably due to a breach in the integument and the localization of $CD4^+$ lymphocytes and macrophages in an ulcer. Thus, they serve as efficient transmitters of HIV in those infected or as available targets for infection in those exposed.

The acquired immunodeficiency syndrome (AIDS) epidemic has reminded modern clinicians that *T pallidum* invades the central nervous systems of a large number of patients with early syphilis. Further, there is increasing evidence that neurologic manifestations of syphilis are more frequent in persons with both syphilis and HIV and that neurorelapse after standard benzathine penicillin therapy for syphilis is not uncommon in patients with HIV infection. Today's physicians face the difficult problems of determining which patients require lumbar puncture for the detection of central nervous system syphilis, of interpreting nonspecific cerebrospinal fluid (CSF) findings—such as pleocytosis and increased protein concentration—in patients with HIV, and of choosing optimal therapy. It has been recognized for years that standard therapy with benzathine penicillin fails to provide measurable penicillin concentrations in CSF, but until HIV, the weaknesses of standard therapy were not appreciated. And until recently, syphilis experts were confident that the more intensive therapy recommended for neurosyphilis would still be effective. Disturbing new reports suggest, however, that even high-dose intravenous penicillin G fails to cure neurosyphilis in some HIV-infected patients,[2,3] prompting some experts to speculate that microbiologic cure may not be possible in these patients.

At the height of the most recent epidemic in 1990, the rate of infectious syphilis in the United States was higher than at any time in the past 40 years, and the number of infants born with congenital syphilis soared. With the exception of its prevalence in several northern cities such as St Louis, New York, and Chicago, syphilis is a disease that is concentrated in the South, increasingly in rural areas.[4] Public clinics, which provide most syphilis care, are overcrowded, often closing their doors to new patients before noon, and are unavailable or inaccessible to many rural inhabitants. The racial distribution of syphilis further complicates focused efforts to control the disease. The rate of infectious syphilis in African Americans is 60-fold higher than in whites, yet neither poverty nor the reporting bias from public clinics can account for this disproportionality, as the rates in other minority groups demonstrate: the rate in African Americans is still 17-fold higher than that in Hispanics and 30-fold higher than that in Native Americans. The fact that we are aware of the disproportionate burden of syphilis in African Americans, yet fail to act, serves as evidence that racism or, at least, indifference exists in health care in this country. Intensive and focused public health approaches are desperately needed to control syphilis, yet these approaches must avoid stigmatizing the target populations, and they must earn the trust and cooperation of the patients. The specter of the Tuskegee study of untreated syphilis in rural black men, conducted by the US Public Health Service from 1932 to 1972, still affects the acceptance of public health efforts by many African Americans.[5]

The United States stands out as the only industrialized country that has failed to control syphilis. Since the mid-1950s when targeted and successful antisyphilis campaigns were eliminated, the public health response to syphilis has been reactive, rather than proactive. It is only when the incidence of infectious syphilis rises alarmingly that increased funds for case identification and control are

made available. When the number of cases declines, so do funds, setting the stage for yet another outbreak. This cycle has occurred repeatedly in the past four decades, and we can expect it to continue unless we recognize and seize the opportunity to make a change. Syphilis is a disease that we can easily detect using inexpensive blood tests and can treat with an economical and readily available drug. The scientific means are available to control this infection, and financial resources could be made available; only the will is lacking.

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Lessons From the Practice

Inspiration for a Tired Medical Student

MARK O. GOODARZI, *San Francisco, California*

It's all too easy for a second-year medical student to drown in the ocean of work that is so typical of the year. When this happens, the medical school experience becomes just hours of study and endless examinations. I was having this "drowning" feeling during midterm time when one of those clinical experiences occurred that for preclinical medical students is like glimpsing a life raft on the horizon.

That week I had two exams. On Monday afternoon, after the first one, I went to the internist's office where I did my weekly preceptorship. I was anticipating a typical afternoon of following her around and picking up clinical pearls. Instead, one of her patients had been admitted to one of the hospitals in San Francisco, and she wanted me to go there and to obtain as much of a history and physical examination from the patient as I could. She would come by an hour or two later and hear my report. I could feel my heart rate increase at the prospect of seeing a patient entirely on my own. Nervousness turned to excitement as I jumped into a taxi and headed to the hospital.

I had never been to this particular hospital. When I got there, I donned my white coat and went looking for the information desk. I marveled that this simple garment, the white coat, with a penlight and stethoscope hanging off it, gave me enormous privilege. As I walked through the hospital lobby, I noted the respect and power afforded me by my membership in the medical profession, and I felt a great sense of gratitude and responsibility.

I found the patient's room and politely introduced myself to her. She was an 80-year-old woman suffering from an acute attack of dyspnea due to pulmonary edema. Also in the room were her daughter and two sons, all much older than me. Interacting with these four people was sheer pleasure. Mostly we talked about what was happening to the patient and her past medical history. I was awed by the fact that I, a total stranger, could walk into this room and instantly have the trust of this family.

I was performing a simple physical examination on her when a team, consisting of an attending physician, an intern, and a couple of residents, arrived. I was brushed aside as they proceeded to do a history and physical with lightning speed. The family appeared a bit intimidated by the attending physician as he authoritatively fired off question after question. The examination was quickly and efficiently done, with little time spent to establish a doctor-patient relationship. Their manner bothered me, and I made a vow that I would never see a patient without first addressing her and her family's needs.

After the team left, I decided to abandon the rest of the physical as I did not want to put the patient through any further exertion. We talked some more until I felt that I had gotten a complete history, and then I left. At the nurses' station, the team was discussing the patient's case, and, much to my relief, they were expressing concerns for her welfare. It was unfortunate that the time available to acquire the information needed and to teach the residents did not leave the physician time to show his concern to the patient while he was with her. I sat down and absorbed as many of the technical details of her case as I could.

Shortly after the team left, my preceptor arrived, and I presented the case to her. She told me she was proud of my presentation and reminded me of how far I had come since my first attempt to present a case. We then thoroughly discussed the details of the patient's illness, and I was gratified to realize that I could actually apply some facts and concepts after all the arduous hours of study. I also enjoyed being able to have this discussion with my preceptor as equals.

Finally we went to see the patient and her family. My preceptor thanked them and explained her role in my education. One of her sons responded by saying that it had been a pleasure talking to me, and the other said that I had a great "bedside manner." The patient herself said that talking with me had been very comforting. Their comments lifted my sleep-starved spirits, and suddenly I realized why I had been staying up past 2 AM night after night. All the studying and examinations were helping me become a physician, and being a physician meant having the ability to share in the lives of others and to bring them comfort. I found myself smiling as my preceptor chatted with the patient and her family, and I witnessed their mutual respect, trust, and friendship.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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(Goodarzi MO: Inspiration for a tired medical student. West J Med 1995; 163:589)

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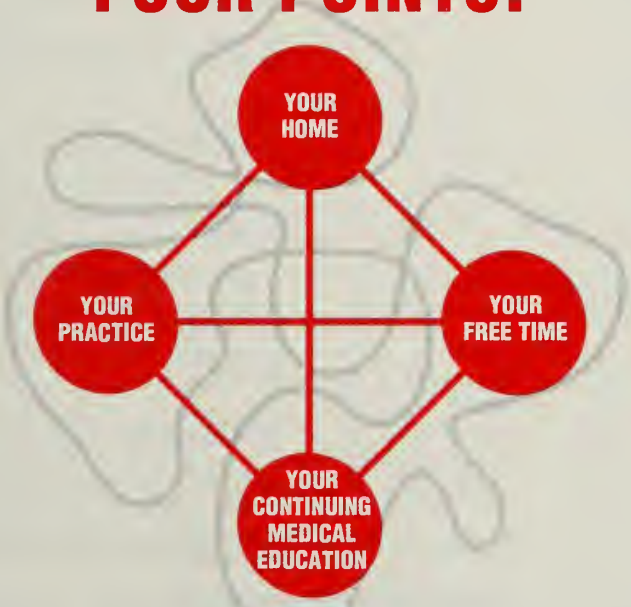

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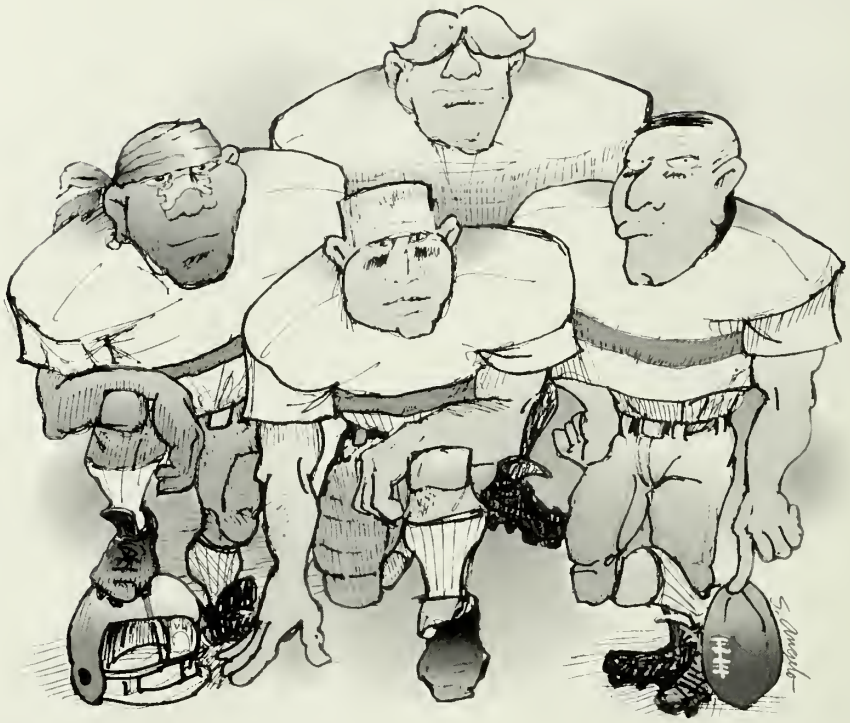

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A SUPPLEMENT TO
The Western Journal of Medicine

Editor's Introduction

Pioneering is an adventure. In this volume, THE WESTERN JOURNAL OF MEDICINE's first supplement, we publish the Henry J. Kaiser Family Foundation's pioneering efforts in exploring the challenges and opportunities of reproductive health and managed care as they adjust to each other. Versions of these papers were presented at a November 1994 Foundation conference on the subject.

The special editors of this supplement, Suzanne Delbanco, MPH, MPP, and Mark Smith, MD, MBA, have worked diligently with the authors to refine their presentations for print. We are grateful to all involved for their perseverance and dedication. We are also grateful to the Henry J. Kaiser Family Foundation for providing the funds for this supplement, which will have a wide distribution beyond the usual 45,000 *WJM* subscribers. It is good to have vigorous, farsighted partners in pioneering.

LINDA HAWES CLEVER, MD
Editor

Contents

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Reproductive Health and Managed Care

An Overview

SUZANNE DELBANCO, MPH, MPP, *and* MARK D. SMITH, MD, MBA, *Menlo Park, California*

The term "managed care" has come to mean many things. In its loosest form, it might refer to the imposition of preauthorization requirements before patients are admitted to the hospital or undergo expensive diagnostic or therapeutic procedures, utilization review of physician decisions, and restrictions on which physicians may be consulted by patients enrolled in a certain plan. In this sense, it is increasingly difficult to find *any* care in the United States that is not "managed."

Increasingly, however, managed care has also come to mean any one of a variety of organized mechanisms for the enrollment of patients, the selective contracting of physicians, and the building of a culture of physician practice (whether by sharing a location and tight administrative integration or use of financial incentives and performance feedbacks, or both). These mechanisms increasingly dominate the provision of health care in the United States. The most tightly organized of such systems are health maintenance organizations (HMOs), which continue to exhibit dramatic growth (Figure 1).

By the end of 1994, more than 50 million people were receiving their care in approximately 574 managed care organizations. This represents an increase in membership of almost 50% since 1988 and 300% since 1983. The highest growth has been on the West Coast, in New England, and in the mountain states. California has more than 12 million persons enrolled in managed care organizations. The penetration of HMOs varies by region of the country (Table 1).[1]

Many HMOs are large organizations, as a result of both growth and consolidation. California, Minnesota, and Massachusetts, the most mature markets for managed care, have undergone a wave of mergers and consolidations in recent years. This activity is driven by twin pressures to keep down prices and a growing demand for value—quality for money paid—by the purchasers of care. Although these trends started with private employers, state and federal governments are now actively involved in the same quest. As a result, previously established relationships in the health care system are changing. And providers, which in the past have depended upon patients selecting them for care (including not only family planning agencies and obstetricians, but also many other specialists and hospitals), are finding that organizations that control "covered lives"—and thus patient flow—are controlling access.

Indeed, the unevenness of the changes sweeping the marketplace is one of the principal features of the current period. The circumstances prevailing in any local area may be unlike those of others and may develop along different paths.

Reproductive Health

Reproductive health, which is also often discussed but rarely defined, inspires passions in many people; the term has, however, no clear and common definition. For our purposes, reproductive health services include services needed by women and men in their childbearing years, traditionally defined as between the ages of 15 and 44, although some might argue that these services should start at age 11 or 12 and extend later.

Men have reproductive needs: contraceptive counseling, sterilization, and screening for testicular cancer and sexually transmitted diseases (STDs), including the human immunodeficiency virus (HIV). This discussion, however, centers on services needed by women because the responsibility for and use of contraception are largely in the hands of women. Public funding sources, specialists, and institutions are available that focus entirely on women's reproductive needs in a way that they do not focus on men's. We define reproductive health services to include the following:

- Preconception risk assessment and care
- Prenatal care
- Labor and delivery
- Postnatal care
- Family planning, or contraceptive services and supplies
- Voluntary contraceptive sterilization
- Screening for cancers of the reproductive system
- Diagnosis and treatment of infertility
- Abortion
- STD diagnosis and treatment
- HIV screening and diagnosis
- Routine gynecologic examinations

Although STDs may not be included in some definitions of reproductive health, the two areas are closely linked. Women infected with STDs are at risk for cancer and infertility; STDs also create serious conditions for the fetus and the infant at birth. Basic infertility services are included because they may relate to a couple's or individual's ability to choose to become pregnant and

(Delbanco S, Smith MD: Reproductive health and managed care—An overview. West J Med 1995; 163[suppl]:1-6)

From the Henry J. Kaiser Family Foundation, Menlo Park, California.
Reprint requests to Suzanne Delbanco, Program Officer, Kaiser Family Foundation, 2400 Sand Hill Rd, Menlo Park, CA 94025.

ABBREVIATIONS USED IN TEXT

ACOG = American College of Obstetricians and Gynecologists
HIV = human immunodeficiency virus
STD = sexually transmitted disease

because, in many cases, problems associated with infertility can be diagnosed and reproductive capacity restored relatively easily.[2] Each of the included services is important in its own right and is significant in its relationship to the others.

Although many reproductive health services are preventive, for a variety of unique reasons they may not fit neatly into the preventive strategies of managed care. Managed care systems often entail intake procedures that, by design, restrict direct access to specialized care. Although such approaches seek to direct patients to appropriate and cost-effective sources of care, definitions of appropriate care may be subject to the opinions and values of the gatekeeper, whether an individual or an institution.

The social acceptability of abortion and some infertility treatments varies widely. Furthermore, the patient most often identifies her or his need for reproductive health services in accordance with certain personal or social goals; these services may be more intertwined with a patient's ethical and religious beliefs than other services. The health care professional is less likely to determine a medical need because the initiative and decision making rest with the patient. Only the patient can decide whether to engage in sexual relations without risking pregnancy, to avoid the consequences of an unplanned pregnancy, or to become pregnant at a chosen time. Because reproductive health services are likely to be personal and socially sensitive, they may require special protection regarding the confidentiality of the services and the circumstances in which they are delivered.

Who Delivers Reproductive Health Services and What Do They Have at Stake?

Providers of reproductive health services stand to be affected profoundly by the changing health care system. Providers include a broad range of primary care providers and specialists, operating in settings that vary from publicly funded family planning and women's health clinics to medical offices of for-profit staff-model HMOs. Private-sector sites may include HMOs, group practices, hospitals, and private practices. Publicly funded sites include categoric clinics such as abortion, family planning or STD clinics and community health centers, hospital clinics, and public health departments. Both generalists and specialists offer services in obstetrics and gynecology, family practice, and internal medicine. They may be physicians, nurse practitioners, or physician assistants.

The role for the practice of obstetrics and gynecology may be changing. A study that forecasted the effects of managed care growth on the US physician workforce found that the current ratio of obstetrician-gynecologists

TABLE 1.—*Regional HMO Penetration: Year End, 1994*

Region	*HMO Enrollment, %*
New England	27.5
Middle Atlantic	21.9
South Atlantic	15.3
East North Central	17.8
West North Central	14.6
South Central	9.3
Mountain	22.0
Pacific	34.9

From Group Health Association of America.[1]

to patients was slightly less in managed care organizations than in the United States in general. It also found that a large percentage of outpatient obstetrics and gynecology visits can be provided by nonphysician providers.[3] With the growth in managed care, these ratios are likely to be decreased. In this way, the operations of managed care and family planning organizations may become more compatible. Much is at stake in the evolution of relationships among different providers, especially between managed care organizations and family planning organizations.

For managed care organizations, reproductive health services provide challenges for delivering efficient and effective care. After all, these may be the only services used by most of an organization's members. The quality of these services, from a patient's perspective, may have a major influence on whether an organization retains the membership of that patient.

In managed care plans, especially HMOs, primary care physicians are usually the point of entry into the health system. These gatekeepers provide primary and preventive care and manage the referral of other services available to members, such as specialty care and hospital

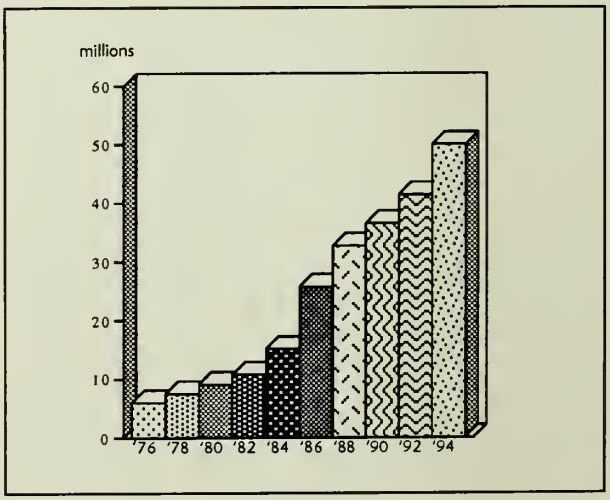

Figure 1.—The number of Americans receiving care in an HMO, 1976 to 1994, is shown. From Group Health Association of America.[1]

admissions. Managing the flow of patients in this way is thought to emphasize prevention and primary care and reduce unnecessary use of more expensive specialty care. But do obstetricians and gynecologists practice primary care? The American College of Obstetricians and Gynecologists (ACOG) has endorsed changes in training programs to increase training for obstetricians and gynecologists in primary care for women. Furthermore, some states have designated obstetricians and gynecologists as primary care providers; others have not. These designations influence whether or not these physicians can act as gatekeepers. A survey conducted by ACOG in 1993 found that 75% of women disapprove of a system that requires a referral to have access to an obstetrician or a gynecologist.[4] This has implications for patient satisfaction and member retention.

The vast majority (81%) of HMOs allow patients to self-refer to obstetricians and gynecologists one or two times each year or to have an obstetrician-gynecologist as their primary care provider (see article by Bernstein and colleagues, pp 15-18).

The growth of managed care has important implications for organizations providing specialized services that are not now part of organized systems of care. Family planning clinics, school-based health programs, and other public providers increasingly depend on Medicaid for their financial viability. Indeed, Medicaid now pays for a greater proportion of family planning services than does family planning-specific funding in Title X, which provides categoric funding for more than 3,900 family planning providers who serve more than five million low-income patients each year.[5] As increasing numbers of Medicaid recipients are enrolled in managed care organizations, the survival of fee-for-service providers is at stake. Many family planning agencies want Medicaid dollars to be "carved out" so that Medicaid recipients can freely seek family planning services from any Medicaid-qualified provider, even if they are enrolled in a managed care plan (see article by Rosenbaum and colleagues, pp 33-38). In 1992, 19 states had enrolled 10% or more of their Medicaid recipients in managed care plans.[6] Two of these states, California and New York, have the biggest Medicaid populations and the most ambitious plans in the United States. Both expect to enroll a majority of their Medicaid recipients in managed care plans by 1997. Although a federal mandate ensures that enrollees in certain types of Medicaid-supported managed care may seek family planning services from any Medicaid provider (perhaps protecting both the enrollees' confidentiality and the viability of many family planning organizations), 14 states currently have an exemption from this provision.

These categorical providers fill a unique and important niche. The established network of family planning clinics and organizations has been instrumental for decades in providing care to people for whom other providers are unavailable or unattractive. The extent to which they are a source of care for patients already enrolled in managed care plans is unknown.

Similarly, the network of freestanding facilities performing abortions plays an important role. These clinics provide 86% of all abortions done in the United States each year. Other abortions are generally done either in hospitals or physicians' offices at higher cost.[7]

Furthermore, women and men seeking screening and treatment for STDs can find publicly supported care at a network of clinics devoted specifically to these services. It is unknown how many people using these sites for care have insurance and access to care elsewhere. To the extent that they do, these and other publicly supported health services are subsidizing managed care organizations. Is it possible that they provide a unique set and style of services that managed care organizations should be buying for their members?

Goals and Objectives of Managed Care

Several of the main goals and attributes of managed care have implications for the delivery of reproductive health services.

Comprehensiveness

Managed care plans provide a broad range of care, including physician services, hospital stays, and other services required to prevent, diagnose, and treat illnesses and maintain health. Plans provide these services through networks of delivery that vary in how they are linked organizationally, geographically, and financially.

Comprehensiveness should, at least theoretically, improve the integration of reproductive and nonreproductive health services. For example, a physician who discovers a nonreproductive condition requiring treatment while performing a pelvic examination would be able either to treat the condition or to refer the patient to another physician within the same organization for treatment.

Coordination of Care

Coordination of care is the managed care plan's process of ensuring that effective linkages exist among providers for a patient at a given time. Furthermore, depending on the involvement of a gatekeeper, both primary and specialty care are tracked by the clinician charged with guiding the member through the system. To the extent that a patient's reproductive health is connected to other facets of health, this kind of coordination may be advantageous. Likewise, it is difficult for categorical providers, such as family planning organizations, to coordinate care that goes beyond their competencies and to track patients receiving care in other, unrelated venues.

Continuity

Continuity of care ensures that effective links exist between providers over time. For example, a woman's contraceptive needs often change as she ages. The appropriateness of care varies with a woman's opinions on family size, her medical needs, and her social life. Presumably, if a provider has cared for a particular patient consistently over time, that provider's ability to match the patient's reproductive desires with an appropriate method of contraception would be enhanced.

Most managed care plans attempt to develop extensive management information systems that track the use of services and enable providers to review the range of services given members receive during their tenure with the plan.

Cost-Effectiveness

Controlling health care costs by controlling inappropriate utilization of resources is one of the principal aims of managed care; its achievement would be a benefit to both the individual patient and society. Managed care organizations of different types use different strategies to control costs, including intensive utilization review, feedback to individual physicians comparing their practice patterns, and increasingly sophisticated financial incentives to physicians for a style of practice that the organization deems appropriate. In addition, fostering a culture supportive of appropriate care through practice guidelines and periodic conferences provides further incentive for cost-effective behaviors.

Other basic strategies attempted by some managed care organizations are selective contracting with efficient providers and limits to patient self-referrals.

Population-Based Approaches

Many of the services included in our definition of reproductive health have public health goals and implications, such as screening for reproductive-tract cancers and control of STDs. Part of the rationale for governmental public health functions is the inability of a system based on individual practitioners to have the scale and scope to be competent in tackling population-based problems. The growth of large managed care organizations now calls into question our sole reliance on public mechanisms to carry out such tasks. If, for instance, an HMO has 80,000 or 100,000 members in an area, it likely has the capacity and the interest to assume a population-based approach to issues such as outreach for prenatal care or education to reduce the spread of STDs, which may have costly health sequelae. Theoretically, at least, the increasing consolidation of managed care organizations into a few large systems should provide greater capacity for the private medical system to carry out public health goals.

Improving Quality

Managed care organizations have substantial experience in the development, testing, and application of quality measures; this experience should translate into better quality measures in reproductive health as well.

The quality of reproductive health services may be difficult to measure in any setting. Counseling, for example, may be the most important element in preventing unplanned pregnancy. But it has been difficult to demonstrate that counseling has a direct causal effect on effective contraceptive use (see article by McGlynn, pp 19-27). Long-term quality measures are also difficult in settings in which patient enrollment is brief, as may happen when a patient changes jobs or visits a family planning organization once in an emergency situation and does not return.

As examples, both hysterectomy and cesarean section are reproductive health services whose incidence varies drastically, depending on the availability of specialists. Care may be improved by establishing explicit criteria for surgical procedures and by monitoring and imposing sanctions on providers who perform unnecessary or inappropriate procedures.

This difficulty in measuring quality poses special challenges for organizations that are considering contracting services from or merging with other organizations and want some means by which to assess their potential partner.

Elimination of Incentives to Overtreat

One of the hallmarks of the fee-for-service system is that it inherently offers incentives for providers to do more, rather than less. In combination with other factors, such as professional training and medical culture, this has led to numerous instances of the overuse of diagnostic and therapeutic procedures. Reproductive health has, in fact, provided many examples of such overuse, including vast variations in rates of hysterectomy and cesarean section that are unjustified by rational medical practice.[9,10] Although there is legitimate concern about the reversal of incentives implied by managed care (incentives may now be offered to undertreat), the care of patients—and particularly of women—should be improved by the removal of incentives to perform such unnecessary procedures.

Potential Disadvantages of Managed Care

Several reasons have been cited for optimism about the growth of managed care. Nevertheless, several features of the developing system are causes for concern.

Lack of Confidentiality

Confidentiality is more important in reproductive health than in other types of medical care. The sensitivity of some of the specific services involved—sterilization, abortion, contraception, screening and diagnosis for STDs, infertility diagnosis and treatment—may make patients reluctant to let employers or family members know of the services they have sought or received. In some instances, confidentiality might also be a concern for a woman seeking maternity care early in pregnancy, before her pregnancy becomes evident.[11]

Concern about confidentiality may, in effect, reduce access to reproductive health care services, especially for sexually active teenagers, because eligibility is based on the family unit. It may be difficult for members to obtain confidential care when they must have access to the family's insurance card or have a claim signed or submitted by the policyholder (usually the parent).[2] For example, in an environment where providers and administrators seek information from a common management information system or where referral for specialized services is required, it may be difficult for a teenager to obtain an abortion within the health plan without the knowledge of her family physician.

Organizational Vulnerability to Ideologic Pressure

As managed health systems become larger because of growth and mergers, organizational ideologies affect greater numbers of health professionals and patients. Health care providers may be pressured by the organizations that employ them to withhold the provision of particular services, such as abortion or contraception. Systems sponsored by the Catholic church are a striking example.

Catholic hospitals account for 16% of all US hospital admissions, inpatient days, surgeries, payrolls, and expenses. Of these hospitals, 71% are affiliated with one of the 66 Catholic health care systems. These networks include hospitals, HMOs, and laboratories that are owned or managed, or both, by the Catholic church.[11] All Catholic health care facilities are subject to church doctrine, not only in the area of institutional financing, but also with regard to service provision.

These institutions are a special case because they decline to provide some services. Operating under the "conscience clause," Catholic networks follow the guidelines of the National Conference of Catholic Bishops' Ethical and Religious Directive for Catholic Health Facilities. The directive prohibits abortion, contraceptive sterilization, provision of contraceptive services and supplies, most forms of assisted reproduction, and, in most cases, the "morning-after pill" for rape victims, although some information and referral may be provided in these areas (see commentary by Bayley, pp 71-72).

The presence of a group of health care providers that limit care in this way poses unique problems in reproductive health. Patients rely on their health professionals for information about health maintenance and care options. If certain types of information are being withheld, many may not know what questions to ask or recognize the incompleteness of what they are told. People who live in areas with a limited selection of health care providers or lack the money and means to seek out and use a competing provider may be limited in their choice of care and be subjected to the ideologic or religious biases of the provider's organizations.[12]

Incentives to Undertreat

Without methods to monitor quality, exchanging incentives to overtreat for ones to undertreat is no bargain. The potential downside of influencing behavior by financial incentives is that a focus on the cost of care may place insufficient emphasis on the quality or appropriateness of the care delivered.[12] Because providers in a managed care setting are judged partially on their ability to contain costs and provide appropriate care, they may err on the side of frugality. This might be manifested in less frequent Pap tests or curtailed contraceptive counseling sessions.

Tensions Between Costs and Effectiveness

Theoretically, cost pressures could lead to incentives for health professionals to reduce the provision of, or perhaps promote less aggressively, services that are less actively demanded by patients. The delivery of many basic preventive services in reproductive health care may not be driven by patient demand. Annual Pap tests and mammograms are, perhaps, less apt to be actively demanded by patients than contraceptive coverage or treatment for infertility and, therefore, are less likely to be influential in determining patient satisfaction.

Obstacles to Closer Cooperation Between Providers

Although managed care and family planning organizations have much to learn from each other, working together poses many challenges to both; their cultures are different. Managed care organizations—especially those that are for profit—generally have business-oriented missions, focusing on counseling and direct and timely access to care. Although the emphases may differ, patient satisfaction and financial viability are essential to both.

Problems With HMOs Classifying Family Planning Providers

Managed care organizations generally have providers of two types: primary care providers and specialists. Although primary care has come to mean many things in the wider health lexicon, it has a fairly specific meaning within HMOs. Primary care providers are physicians (and occasionally others, such as nurse practitioners) who are expected to handle a wide variety of patient complaints and conditions, such as hypertension, diabetes mellitus, back pain, minor sprains and strains, coughs and colds, asthma, ulcers, headaches, and the like. They admit patients to the hospital, when necessary, and coordinate inpatient and outpatient referrals to specialists of various types. They are often at some financial risk (as individuals or as a group) for their use of specialist and hospital services.

Although some family planning clinics have expanded their scope of services to handle some of these duties, rarely, if ever, have they been in the position of meeting all of these criteria. And although family planning agencies do perform some of the functions of obstetricians and gynecologists, such as administering Pap tests, STD screening and treatment, contraceptives, and prenatal care (many managed care systems expect primary care physicians, especially family practitioners, to perform most or all of these functions), other obstetric-gynecologic services—labor and delivery, colposcopy and gynecologic surgical procedures, for instance—are usually beyond their purview.

As a result, most Planned Parenthood and other family planning agencies, although perhaps thinking of themselves as "primary care providers" because they are often their patients' first contact with the health system, fall into *neither* category according to HMOs. They offer a package of services that has no analogue among HMO providers. Therefore, considerable rethinking and accommodation would be required by HMO operational and financial structures if family planning agencies are to be part of their network of providers.

The Question of Control in Managed Care Systems

Because of the differing finance systems, the incentive systems in managed care and family planning organizations are, in some ways, opposite. Managed care plans operate within set budgets tied to the number of people they serve. Any efficiencies they can create within their systems yield profit or "surplus." On the other hand, fee-for-service systems incur revenue for each service provided—the incentive, then, may be to provide services, especially those that bring in the most revenue.

Managed care entities can also contract with a reproductive health care provider, such as an existing family planning clinic in the community, from whom a patient can seek services without needing to go through a gatekeeper. These reproductive health care providers could even function as entry points into the managed care system by providing reproductive health services directly and referring patients elsewhere in the plan as appropriate.

In addition, managed care providers, especially staff-model providers, may be opposed to contracting services from external providers. Obstetricians and gynecologists within a managed care organization may view a contract with a family planning clinic as a threat to their control or income.

Differing Clinical Approaches and Standards

The standards of care that health care providers have established for reproductive health differ. Planned Parenthood, ACOG, the federal Health Resources and Services Administration (for Title X grantees), and managed care plans each have their own standards of care (see article by Barnes and colleagues, pp 28-32). If health care professionals are to provide integrated care, the challenge is to create a set of standards that includes a common language. This is especially difficult because providers of reproductive health services, such as private obstetricians, HMOs, and family planning clinics, have entirely different incentives, cultures, and even vocabularies. Reaching consensus on standards might create an environment favorable to expanding contractual and operational cooperation among managed care plans and traditional family planning providers.

Further difficulties are likely in combining operations because of differing management information systems, billing procedures, and staffing patterns. The integration of each organization's interests in patient care is more than a trivial task.

Conclusion

Managed care is changing the way services are delivered, and its presence is growing rapidly. How will reproductive health services be delivered in the growing managed care environment, and how will traditional providers of reproductive health services fit into that environment? The course of reproductive health service delivery will likely reflect local differences in managed care penetration and the adaptability of particular family planning agencies. It is unlikely that all family planning organizations will expand their services to include a full range of primary care. It is possible, in some settings, that family planning organizations will limit their role to providing abortion services on contract or caring for the poor. In some cases, however, the survival of family planning agencies may depend on their ability to work with managed care organizations.

On the other hand, as managed care organizations face competition, they may have much to learn from family planning agencies that could help them compete in the current business environment. Rather than gaining this edge through contracting with these agencies to provide services, however, managed care plans may decide to duplicate the appealing attributes. For example, in the past, discrete models have existed for clinics managed by Planned Parenthood, HMOs, and hospitals. Now, some HMOs and hospitals are moving away from their traditional physician-based clinic model and embracing the Planned Parenthood approach of mid-level practitioners and cross-trained counselors. Duplication allows the managed care organization to maintain more control over quality and utilization than it could with services it contracts. In business terms, this choice between duplication and contracting of external services is commonly referred to as a "make or buy" decision. In many cases, as these providers reorganize care in response to the changing health care environment, the separate models will evolve toward the same goal of multifunction obstetrics and gynecology and primary care clinics that use cross-trained staff (see article by Bernstein and colleagues, pp 15-18).

The effect of this new environment on the delivery of reproductive health services is the subject of the articles that follow.

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Reproductive Health Care Delivery

Patterns in a Changing Market

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Providers of reproductive health services, including clinics and office-based physicians, face new challenges as the American health system progresses toward managed care. Although services for low-income women are often subsidized, the average out-of-pocket payments for reproductive health services are the same for women with incomes below and above 200% of the poverty level. Although many women, especially those classified as low income, use clinics, most say that they would prefer to receive care in a private physician's office and in a place where they can get general health care as well. Multivariate analyses indicate the importance of type of insurance and source of primary health care in affecting a woman's selection of her reproductive health care provider. Specialized providers such as family planning clinics need to consider how they can blend with managed care plans.

(Sonenstein FL, Ku L, Schulte MM: Reproductive health care delivery—Patterns in a changing market. West J Med 1995; 163[suppl]:7-14)

Major forces are reshaping the health care market in the United States. Providers of reproductive health care, including clinics and office-based physicians, are confronting the challenges of cost containment and managed care. Simultaneously, they are trying to address issues such as new contraceptive technology, epidemics of sexually transmitted diseases, including the human immunodeficiency virus, and the politics of contraception and abortion. We will try to set the stage for a discussion of changes in the health care system by presenting data about how reproductive health services are currently delivered in the United States.

Reproductive health care is a central component of health services for women. In 1993, an estimated $41 billion was spent on reproductive services for women aged 15 to 44 years, about a third of all health expenditures for women of these ages (Figure 1). Pregnancy-related health care makes up the largest portion of reproductive health care expenditures, about $25 billion (60%), whereas contraception and abortion services account for $1.5 billion (4%) and other reproductive services (such as routine gynecologic examinations, Pap tests, infertility testing and treatments, and treatment for diseases related to a woman's reproductive system) account for $15 billion (36%).[1]

In this article we focus on nonpregnancy-related reproductive health services—contraception, abortion, and other reproductive services such as cancer screening—which comprise about 40% of all reproductive health care expenditures and about 13% of all health care expenditures for women between the ages of 15 and 44. We address these questions: Where do women get reproductive health care? How do women pay for their reproductive health care? Where would they prefer to receive care? What factors affect the type of setting that women use?

Where Women Obtain Reproductive Health Care

Insurance Coverage

Over the past two decades, the changing levels and types of insurance coverage have affected women's reproductive health care coverage and, consequently, their health care choices and utilization.

Data from the National Health Interview Surveys indicate that the level of uninsurance has increased in recent years. The age-adjusted uninsurance rate for nonelderly women rose from 12.2% in 1980 to 14.9% in 1989 to 16.3% in 1992. In comparison, the uninsurance rate for nonelderly men was lower than that for women in 1980 but exceeded the women's rate by 1992 (men: 7.7% in 1980 and 18.2% in 1992).[2] Data from the Current Population Survey yield slightly different results: Nonelderly white women had the same level of uninsurance in 1992 as in 1988 (13%), but black women's uninsurance rate declined from 19% in 1988 to 17% in 1992. In contrast, white men's uninsurance rate climbed from 15% in 1988 to 17% by 1992, and black men's rate stayed constant at 25%.[3] Despite these discrepancies, the factor pushing down insurance rates was the erosion of employer-based private insurance. The decline in private insurance was partially offset by expanded Medicaid coverage, especially for women and

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ABBREVIATIONS USED IN TEXT

HMO = health maintenance organization
PPO = preferred provider organization

children. Because many poor women are not eligible for Medicaid unless they have children or are pregnant or disabled, however, they remain more likely to lack any health insurance coverage. About a third of poor women ages 18 through 64 lacked any health insurance in 1990.[4]

Enrollment in health maintenance organizations (HMOs, including group, individual practice association, and mixed models) has grown in recent years. In 1980, 4.0% of Americans belonged to HMOs, compared to 13.4% in 1990 and 15.1% in 1991.[2] Enrollment has also grown rapidly in preferred provider organizations (PPOs), including point-of-service and exclusive provider organizations.[5] For many years, there was relatively little managed care in Medicaid, but in recent years it has expanded rapidly, growing from 2% of enrollees in 1982 to 24% in 1992 (this includes both capitated HMOs and fee-for-service gatekeeper systems).[6]

Having private health insurance coverage does not necessarily mean that reproductive health services are covered. An inherent problem is that indemnity insurance is rooted in the concept of "medically necessary" services —when a medical disorder is present and requires treatment—and typically offers sparse coverage of preventive health care. A survey of insurance firms found that coverage for routine gynecologic care and contraception varies considerably.[1] For example, the majority (52% to 62%) of indemnity-type plans do not cover oral contraceptives, but HMOs generally do. Coverage of other forms of reversible contraception, such as Norplant or diaphragms, have lower coverage rates, although HMOs are always more likely to cover them than are indemnity plans. About half (42% to 56%) of indemnity plans do not cover annual gynecologic examinations, compared to 31% of PPO plans. On the other hand, HMOs almost always cover these examinations.[7] Coverage of reproductive services can also vary by state because some states mandate coverage of particular procedures. In 1991, for example, 42 states mandated that private insurance cover mammograms and 8 states mandated coverage for Pap tests.[1]

In all states, Medicaid must cover family planning services and is favored with a higher federal matching rate than other types of health care. Even so, it has been estimated that only about half the women on Medicaid who need family planning services actually use Medicaid family planning benefits.[8] Medicaid coverage for other reproductive health services is quite uneven. For example, in 1992 two states provided no coverage for Pap tests; in seven states only Pap tests in family planning or maternity clinics were covered; in five states only the laboratory cost of the test was covered, and in nine states a Pap test was covered only under a physician's order; 27 states covered Pap tests for all women eligible for Medicaid. Coverage for mammography under Medicaid is also uneven: No coverage was pro-

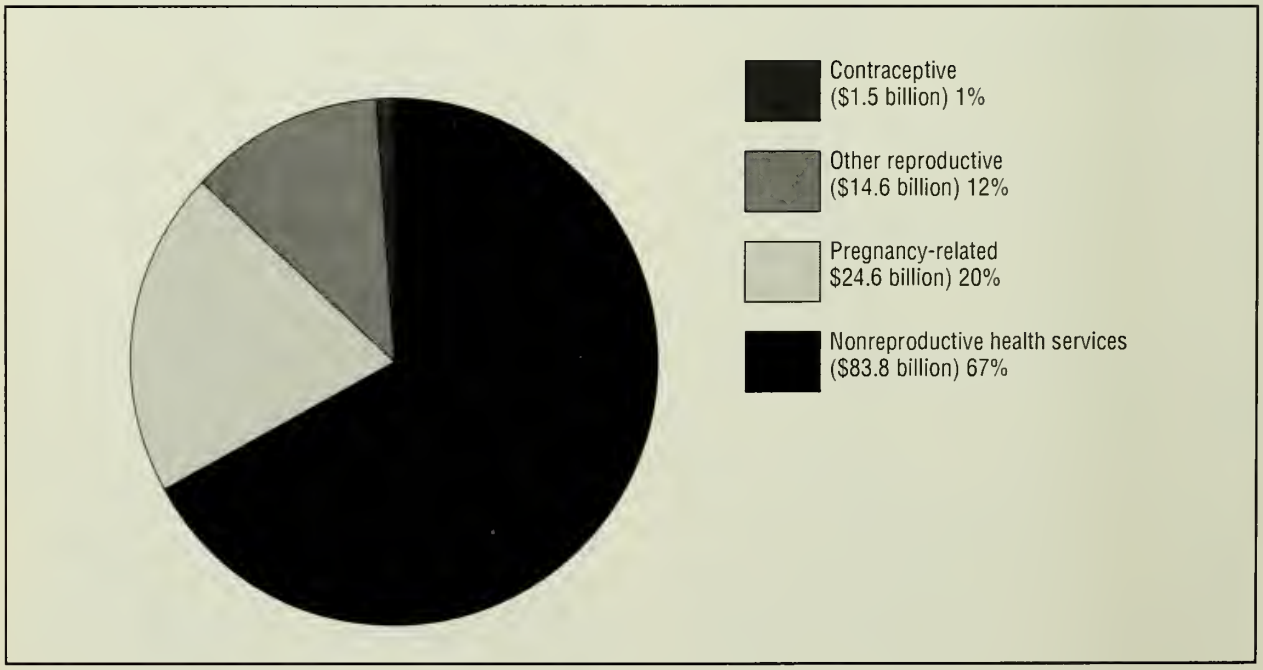

Figure 1.—Expenditures for reproductive services as a proportion of the total health expenditures are shown for women ages 15 to 44 years. Data are based on the 1987 National Medical Expenditures Survey, updated to 1993 levels (from Women's Research and Education Institute[1]).

vided in 12 states, whereas mammography was covered with a physician's order in 15 states, and in 23 states all Medicaid-eligible women were covered.[9]

Use of Services

In spite of the changes noted here, the actual use of reproductive health services among women of reproductive age has remained stable since the mid-1980s, after showing remarkable improvement in the previous decade. Between 1982 and 1988, use of family planning services by women ages 15 to 44 remained stable among low- and upper-income women alike. Nonetheless, in 1988 almost half (45%) of women who were sexually active and fertile and did not want to become pregnant failed to have a family planning visit in the previous year.[10]

Between 1973 and 1985, preventive health screening among women increased. The proportion of women not screened for breast or cervical cancer declined sharply, especially for older women (over age 60) and black women of all ages.[11] Since 1987 the proportion of women older than age 18 who have had a Pap test within the last three years has remained stable. For women beyond their reproductive years (over age 50), the proportion who had a clinical breast examination and a mammogram in the past one to two years has doubled since 1987. Even so, the levels of preventive care may still be below recommended levels: In 1992 about half of women ages 50 to 64 had a mammogram, 60% had a clinical breast examination, and half had a Pap test within the past year.[12]

Who Obtains Care?

Lack of health insurance coverage is a key factor in women's utilization of reproductive health care. Women without health insurance coverage are less likely to have had a recent reproductive health care visit.[1,13-16] Given that different types of insurance have different rates of coverage of reproductive health services (as discussed above), it is not surprising that older women with HMO coverage are more likely to have Pap tests than women in fee-for-service plans. Recent Pap tests are even less common among women on Medicaid and the uninsured.[12]

Evidence also suggests that the type of primary health care provider also affects the receipt of care. Analyses of the 1987 National Health Interview Survey show that 85% of HMO participants had had a Pap test within the previous three years, compared with 75% of women going to private physicians and 74% of those going to other health providers such as clinics. Only 58% of the women with no usual health care provider had a Pap test in the previous three years.[17]

Other health delivery factors affect whether women receive reproductive health care. Women who have a regular source of health care are more likely to have had reproductive care in the past year.[16,18] Women with female physicians have higher rates of Pap tests and mammograms than those with male physicians.[19]

Demographic factors are also associated with the receipt of care. Women are less likely to have received reproductive care when they are Hispanic,[16-18,20,21] never married,[16,20,22] less educated,[1,13,16,18,20] or have a low income.[13,16,18] African-American women have slightly higher rates of utilization than white women. Age is also related to the use of reproductive care. In 1990, 64% of women ages 18 to 29 had had a Pap test compared with 55% of women ages 30 to 44. Older women were even less likely to have had this test. Only 44% of women between ages 45 and 64 and 30% of women 65 years and older had had a Pap test.[4,23]

Surprisingly little has been reported about women's use of other reproductive health services. We present new analyses from a recent survey that enabled us to more closely examine where women receive reproductive health care and the factors that affect these choices.

Data Collection

To answer questions about women's experiences with reproductive health care, we used the 1993 Follow-up of the National Survey of Women. This survey is unique because it collected information about where women obtain reproductive care combined with information about out-of-pocket cost of the last visit, sources of payment, and women's preferences and experiences with the health care provider. The 1993 telephone survey reinterviewed a national sample of women who had been interviewed in person in 1991.

The 1991 study examined contraceptive behavior among women then aged 20 to 38. In 1993 a telephone follow-up survey was conducted to study the adoption of Norplant.[24] A rich array of information had already been collected from the study participants about their contraceptive behavior. Funding from the Kaiser Family Foundation enabled us to add questions to the follow-up instrument that assessed the women's use of reproductive health services and their experiences and preferences. Telephone interviews were conducted between February 1 and April 15, 1993. The follow-up rate of those interviewed in 1991 was 65%. Interviews were completed with 1,093 women between the ages of 21 and 40. This age range does not completely represent women in their reproductive years because teenagers and women in their 40s are not included. As a result, women at the very beginning or end of their reproductive capacity are not covered by these analyses. In addition, the fact that women in the sample aged 27 or older had been part of a 1983 study of unmarried women affects the marital experience of the 1993 sample. The sample is discussed in more detail by Sonenstein et al.[27]

Data were weighted on the basis of age, race, marital status, and educational comparisons with the 1991 sample to compensate for differential attrition and nonresponse. Although the weighting of the sample allows generalizations to US women at these ages, the combined sample may be affected by marriage selection bias and sample attrition.

The following results are based on self-reported telephone interviews. Respondents' recall may be flawed for some of these topics, and respondents may be confused

about certain terms, such as the meaning of "HMO" or "private doctor." (Following the norm of most surveys, we used language that lay people understand, such as "regular doctor" instead of "primary care physician.") Despite these shortcomings, interviews are the only feasible means of collecting data comprehensively for a national sample of women with a variety of insurance and health care arrangements. It is difficult to compile detailed information about patients along with data based on medical records or claims for such a wide array of women, health care providers, and insurers. Thus, these potential recall problems are shared by most of the major surveys in this area, including the National Survey of Family Growth and the National Health Interview Survey. Where feasible, we compared our findings with those from similar surveys, and they were usually comparable. Where possible, we supplement the discussion of our findings with other record-based surveys such as the National Medical Expenditures or Ambulatory Medical Surveys.

Results

In 1993, 80% of women interviewed reported that they had received at least one reproductive health service in the previous year. As seen in Table 1, the most common service received was a gynecologic examination, received by 72% of women interviewed. A third of these women also reported receiving contraceptive services. These findings are similar to those of the 1988 National Survey of Family Growth. In that survey, 71% of women 15 through 44 years of age reported receiving either a Pap test, a pelvic examination, or a breast examination, and 35% had received at least one of the contraceptive-related services shown in the table.[10]

Where Do Women Receive Reproductive Health Care?

Women receive reproductive health care services in a wide range of health care settings, including from office-based physicians with different specialties, family planning clinics, other types of clinics, and staff-model HMOs. More than three-quarters (76%) of women reported receiving reproductive care from private physicians, while 15% went to clinics, 7% went to HMOs,[1] and 2% went to other types of health providers. Poor women were much more likely to use clinics and more affluent women to use private physicians (Table 2).

TABLE 1.—*Reproductive Health Services Received in Past Year for Women Ages 21-40, 1993 (Weighted Percent, N=1,093)*

Service	Reproductive Services (%)
Getting or renewing birth control method	34
Pregnancy test	22
Counseling about a pregnancy	12
Abortion	1
Sterilizing operation	2
Advice or treatment for infertility	4
Treatment for health problem related to birth control	3
Test or treatment for sexually transmitted disease	7
Treatment for a problem related to sexual intercourse	4
Gynecologic examination	72
At least one of the above	80

TABLE 2.—*Source of Reproductive Health Care in Past 12 Months by Income (Weighted Percent)*

Income Level (% of Poverty)	Percent With Any Reproductive Health Visit in Past Year (%)	Source of Care* (Among Those With a Visit) Clinic (%)	Physician (%)	HMO (%)
0% to 100%	68	33	56	8
101% to 200%	74	23	73	2
201% to 400%	82	11	76	13
More than 400%	88	7	86	7
Total	80	15	76	7

*Total includes 14 respondents using other providers.

The sources of reproductive health care in the 1993 survey are similar to those reported in the 1988 National Survey of Family Growth—15% of women ages 15 to 44 years obtaining Pap tests in the previous year got them during family planning visits to a clinic. For low-income women obtaining Pap tests, the proportion using clinics was 32%.[9]

Further information about the types of clinic and physician used by the women is not available from the 1993 Follow-up Survey of Women. Most respondents are unable to differentiate the organizational affiliations of the clinics they visit or the medical specialties of their physicians. The types of clinics that could have been visited include those run by hospitals, community health centers, health departments, family planning and Planned Parenthood agencies, company and school clinics, and sexually transmitted disease clinics.

Information about physician specialties is available from other sources, however. Analysis of the 1987 National Medical Expenditures Survey shows that, among women over the age of 15 with at least one general health check-up visit (which may include nonreproductive tests such as cholesterol measurement) in the last year, 26% went to obstetrician-gynecologists, 36% to general and family practitioners, 14% to internists, 33% to other kinds of physicians, and 9% to nonphysicians. (The sum exceeds 100% because a woman might have seen more than one type of physician. These statistics include health care for women beyond reproductive age.[26])

Analyses of the National Ambulatory Medical Surveys for 1989 and 1990 showed that among visits for obtaining a Pap test, 41% were to obstetrician-gynecologists, 50% to general and family practitioners, and 9% to other specialists. Among visits for the principal purpose of a gynecologic examination, 74% were to obstetrician-gynecologists, 14% were to general and family practitioners, and 12% were to other specialists.[27]

Analysis of these data shows that obstetrician-gynecologists deliver a substantial proportion of

TABLE 3.—*Source of Payment for Most Recent Reproductive Health Care Visit (Weighted Percent)*

Source of Payment	All Women With a Visit* (n=863)	Women at or Below 200% of Poverty (n=232)	Women Above 200% of Poverty (n=559)
Medicaid	7%	19%	2%
Private insurance			
Pays all	24%	13%	28%
Pays some	39%	29%	46%
No coverage/No cost	7%	9%	4%
Self-pay only	23%	30%	21%
Average visit cost**	$30.52	$31.52	$32.20

*Includes 72 respondents whose incomes were unknown.
**Includes those with zero out-of-pocket cost.

physician-delivered reproductive health care, but that responsibility for reproductive health screening is shared with general and family practice physicians and, to some extent, internists.

How Do Women Pay for Reproductive Health Care?

Of the women surveyed, 63% reported that their private health insurance (including HMO plans) covered their most recent reproductive health care visit either partially or fully. A quarter (24%) reported that their health insurance covered the full cost of care, and 39% reported that their insurance paid some of the cost for care. Medicaid covered the cost of the visit for 7%, and an additional 7% reported that they had received free care. Almost a quarter reported that they paid for their last visit solely out of pocket. Because clinics and sometimes private physicians may subsidize care (such as with income-based sliding fee scales), the out-of-pocket costs of these women do not necessarily represent the complete cost of care. Women may be unaware of other public or private funds that subsidize their care.

Low-income women reported higher levels of Medicaid coverage, lower levels of complete private insurance coverage, and higher levels of paying for the visit completely out of pocket than women with incomes of more than 200% of the poverty level (Table 3). Because low-income women are more likely to have to pay for their reproductive health care with their own resources, the average out-of-pocket costs of their reproductive health care visits are about the same as those of higher-income women. That is, the average out-of-pocket costs, including full payments, sliding fees, copayments, deductibles, and free services, were essentially the same for women regardless of income. Although we expected low-income women to have lower out-of-pocket costs because of Medicaid and subsidized care such as Title X, this was not the case. The net effect is inequality of care. Because low-income women have fewer resources available, they must pay a higher share of income for reproductive health care than upper-income women.

Women using different types of health care settings rely on different sources for payment and have different out-of-pocket costs. Among low-income women, those using clinics (public and private) were much less likely to report private insurance coverage for the visit (17%) compared with those using physicians (50%) and HMOs (100%). Low-income women using clinics were about as likely as those using office-based physicians to have Medicaid pay for the visit (23% and 19%, respectively). Low-income women using clinics were less likely to have paid anything out of pocket for the visit (45%) and to have paid less on average ($45) compared with those using physicians ($66). Low-income women using HMOs were the least likely to have out-of-pocket costs (34%) and to have the lowest average out-of-pocket cost ($10) among those paying for care.[27]

What Are Women's Setting Preferences?

Although more than three-quarters of women with a recent reproductive health care visit reported going to a private physician, even more women said that they would visit a private office-based physician if they had their choice. Table 4 shows women's provider preferences by the health setting they used most recently. Women overwhelmingly said that they would prefer to receive birth control and other reproductive health services from private physicians. Only 4% reported that they would prefer HMOs, and 8% said they would prefer clinics.

As expected, those few women preferring HMOs are clustered among HMO users and those few preferring clinics are clustered among current clinic users. More than half of those currently using HMOs or clinics said they would prefer a private physician, however.

When asked why they had chosen a private physician, an HMO, or a clinic as their preference, women said they preferred private physicians primarily because of the continuity of clinicians from one visit to the next or because the quality of care is higher. Clinics, when chosen, were preferred primarily for their low cost and accessibility. Among the few women preferring HMOs, low-cost service was the most popular reason for their preference; other reasons given were that the HMO accepted their insurance and gave better-quality care.

The finding that women prefer to receive care in private physicians' offices does not necessarily mean that women prefer to receive care from physicians, nurse practitioners, or other mid-level professionals, nor does it indicate whether women prefer gynecologists, family practitioners, or other medical specialists. It is plausible that women might prefer gynecologists for some procedures, but want family practitioners for other procedures or nurse practitioners for yet other types of care.

The women interviewed were also asked to choose where they would prefer to get reproductive care: at a place that provides birth control services only; reproductive health care in addition to birth control; or general health care for a wide range of health problems. Most (70%) preferred a place that provides general health care,

TABLE 4.—*Setting Preferred for Reproductive Health Care by Setting of Last Visit (Weighted Percent)*

Setting Preferred	Tatal	Setting of Last Visit Among Those With Visit in Last Year) Private Physician	HMO	Clinic	No Recent Visit
Private physician.	87%	96%	56%	68%	82%
HMO.....	4%	2%	30%	4%	3%
Clinic.....	8%	2%	12%	28%	15%

although a substantial minority (28%) preferred a place that provides reproductive health care in addition to birth control. Given that women overwhelmingly prefer private physicians' offices, their stated preferences for a place that provides general health care for a wide range of health problems should probably be viewed as a preference for care in a private physician's office.

Another question asked whether the women would prefer to go to a place that serves only women, one that serves both men and women, or had no preference. A quarter of women preferred a place that serves only women; three-quarters said either that it did not matter or their preference was for a place that serves both sexes. These views contrast sharply with the way that most gynecologists' offices and family planning clinics operate. A survey of Title X clinics found that in 87% of clinics, fewer than 10% of clients are male.[28] The women's views suggest that most women would find it acceptable to receive care at facilities serving both men and women.

It is important to note that the preferences described here are those of women in their 20s and 30s. The 1993 follow-up survey does not include teenagers. It is plausible that the preferences of teenagers are different because their desire for confidentiality may be stronger than that of older women, and they may prefer to receive care from someone other than the family physician. Nonetheless, the women's stated care preferences could indicate problems for family planning clinics if poor women obtain health coverage that would pay for care from a private physician. In a recent study of Medicaid beneficiaries in Monroe County, New York, for example, participants who switched from a fee-for-service to a prepaid managed care plan tended to switch from clinics to private physicians.[29] Although Medicaid legislation requires that women in managed care plans be permitted to use family planning clinics, these women may prefer private physicians' offices or HMOs. Indeed, the general shift to managed care poses new challenges for family planning clinics and community health centers.[30]

What Influences Selection of a Health Care Setting?

Using multivariate techniques, we examined factors associated with the type of reproductive health care setting that a woman selects: private physician, clinic, or HMO. We were particularly interested in the influence of institutional variables such as availability of insurance, regular source of health care, and availability of health resources, controlling for the effects of demographic characteristics. To assess the effect of provider availability, we also included state-level data on the availability of physicians who could provide reproductive health services and of public funding for contraceptive services.* In conducting these analyses, we divided the sample into groups of women who might be able to use an HMO (those with prepaid, HMO-type coverage at some point during the previous year) and those not able to use an HMO (those with regular insurance, Medicaid, or no insurance). Initial analyses showed that those with prepaid coverage always chose either HMOs or private physicians, whereas those with regular insurance, Medicaid, or no insurance always chose either clinics or private physicians.

In general, the most important factor affecting where a woman receives her reproductive health services is where she receives her regular primary medical care (Table 5). Women who use institutional services (HMOs or clinics) for regular medical care are much more likely to also use them for reproductive health services. Women with no regular source of health care are also more likely to use HMOs and clinics rather than private physicians. Clinics are also important sources of care for women who are on Medicaid or who are uninsured, but women who have regular private insurance are more likely to use a private physician. The supply of primary care physicians on hand for family planning does not notably affect the selection of health care provider.

Discussion

In an ideal world, a woman might be able to select her reproductive health care professional from a wide range of choices and base her decisions on her personal reproductive health needs, alternative clinicians' qualifications, range of services offered, practice styles, and convenience. In reality, a woman's choices are constrained by factors such as the type of insurance she has (or lacks), the affordability of services, and where she receives her primary care.

Type of insurance and site of primary health care profoundly affect where and how women receive reproductive health services. Although health professionals exert considerable effort to offer patients the best clinical skills, women's choice of providers is determined more by structural aspects of providers' health care arrangements. The growth and evolution of managed care in public and private markets and related structural changes will affect physicians, clinics, and other providers of reproductive health services as well as women themselves.

A woman's insurance and choice of providers will strongly influence the actual services she receives. If women's health insurance does not cover certain ser-

*The physician supply data are the number of obstetrician-gynecologists, family practitioners, and general practitioners per woman aged 15 to 44 years, based on 1993 data from the American Medical Association.[31] The level of state family planning funds for contraception (including Title X, Medicaid, and other federal and state funds) per woman aged 15 to 44 years in 1992 is based on data from the Alan Guttmacher Institute.[32]

TABLE 5.—*Logit Models for Use of Clinics or HMOs (versus Private Physicians) for Their Last Reproductive Health Visit (Among Those With a Visit)*

	Used HMO (versus Privote Physicion for Lost Reproductive Heolth Visit, Among Women With Prepoid or Prepoid ond Other Insuronce		*Used Clinic (versus Privote Doctor) for Lost Reproductive Heolth Visit, Among Women With Regulor Insuronce, Medicoid, or No Insuronce*	
	Odds Rotio	*(95% Conf. Int)*	*Odds Rotio*	*(95% Conf. Int)*
Demographic characteristics				
Age	1.04	(0.93, 1.15)	0.97	(0.91, 1.03)
Race (African American)	3.37	(1.27, 8.92)	1.93	(1.02, 3.67
No. of children living with respondent	0.74	(0.39, 1.39)	0.93	(0.72, 1.20)
High school graduation	0.71	(0.07, 7.48)	0.66	(0.29, 1.49)
Percent of poverty level	1.00	(1.00, 1.00)	1.00	(1.00, 1.00)
Marital status				
Cohabitating	1.19	(0.24, 5.84)	2.96	(1.25, 7.00)
Living alone	0.72	(0.21, 2.44)	0.82	(0.38, 1.78)
Divorced, separated, widowed	0.51	(0.10, 2.52)	1.08	(0.42, 2.73)
(Ref: Married)				
Reproductive health needs				
Fertile, sexually active but not seeking pregnancy	1.12	(0.25, 4.96)	2.32	(1.01, 5.33)
Infertile	0.90	(0.13, 6.22)	1.05	(0.37, 2.97)
Pregnant or seeking pregnancy	0.84	(0.11, 6.33)	3.13	(1.07, 9.11)
(Ref: Not sexually active)				
Provider supply				
Family planning grant funds per woman	1.00	(1.00, 1.00)	1.00	(1.00, 1.00)
Primary care physicians per woman	0.70	(0.09, 5.58)	1.36	(0.75, 2.44)
Source of health care				
HMO regular source of care	80.43	(27.37, 236.37)		
Clinic regular source of care			29.47	(15.49, 56.08)
No regular source of care	8.89	(1.30, 62.25)	8.14	(3.79, 17.50)
Insurance in previous year				
Any insurance versus no insurance			0.22	(0.10, 0.48)
Medicaid versus regular insurance			3.68	(1.68, 8.05)
Prepaid only form of coverage	2.79	(1.11, 6.97)		
Sample size	245		616	
Model χ^2 =	151.5 with 16 DF		278.5 with 17 DF	

vices (such as gynecologic examinations or contraceptive pills), then women have limited access to these services. Private indemnity insurance plans are more likely to have such coverage limitations. Limited evidence suggests that women who receive care at HMOs are more likely to use preventive services such as Pap tests. Women attending clinics are more likely to obtain sexually transmitted disease testing or treatment.[10,26] If low-income women transfer to private physicians' offices, they may fail to receive preventive testing or services.

The growing trend toward managed care will probably continue to shape women's reproductive health choices. Physicians or clinics that do not or cannot join managed care plans are likely to have diminished access to patients. Nevertheless, joining managed care plans will lead to a reorientation of providers' services and financial patterns and relationships with other health care providers. Family planning clinics, which have sought to specialize in reproductive health care, especially for low-income or uninsured women, may have trouble realigning themselves with the world of managed care. The growing emphasis of managed care in both Medicaid and private insurance means that family planning clinics need to forge relationships with managed care providers, reconsider the range of services they offer, and look carefully at their market niches. In some cases, they may need to broaden into general primary care centers, whereas in others they might refocus their mission toward specific populations, for instance by specializing as teen clinics. It will be a challenge to ensure that the evolving health care system offers efficiency, choice, and quality and that it is a system that can handle the needs of women at all income levels.

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THE HENRY J. KAISER FAMILY FOUNDATION

Women's Reproductive Health Services in Health Maintenance Organizations

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Access to medical care, including preventive services and treatment, is important to the day-to-day lives, health, and well-being of women and their children. Women in their childbearing years are attracted to health maintenance organizations (HMOs) because of their comprehensive benefits and low out-of-pocket costs and are joining HMOs in large numbers.

As HMOs continue to enroll more people, interest increases in how they provide care to women, including prenatal care, screening for cancer and sexually transmitted diseases, and family planning services. Health maintenance organizations are more likely to cover almost all reproductive services than are preferred provider organizations or indemnity plans.[1]

Women are more likely to seek health care if their out-of-pocket expenses are lower.[2,3] Use of several women's health care services is higher in HMOs than in other types of plans, in part because they provide more comprehensive coverage for these services. Recent research indicates that women enrolled in HMOs are more likely to receive mammograms, clinical breast examinations, and Pap tests than women who are enrolled in indemnity plans, on Medicaid, or uninsured.[4]

The fact that HMOs are more likely to provide and emphasize these services correlates with better clinical outcomes. Medicare beneficiaries were diagnosed at an earlier stage of breast and cervical cancers than Medicare fee-for-service beneficiaries, especially those enrolled in areas with large, mature HMOs.[5]

Using data from a survey of 236 HMO plans, we examine how HMOs cover reproductive services. Although we did not obtain comparable fee-for-service data, our research shows variation in coverage and provision of services among different types of HMOs (staff, group, network, and independent provider association [IPA] models).

Methods

All member plans of the Group Health Association of America (GHAA) were mailed a survey addressing two separate issues: how HMOs treat patients infected with the human immunodeficiency virus and how they provide reproductive health services. This article addresses only reproductive health services. Surveys were mailed to HMOs in February 1994, and the results of all questionnaires returned by March 25, 1994, were compiled. Of 353 GHAA members, 236 (66.9%) responded. Members of chains were less likely to complete the questionnaire than independent members (55.6% versus 84.6%). Because we are interested in how plans cover women's reproductive services, data presented here are unweighted and all plans are given equal weight, regardless of enrollment.

Results

Reproductive Services Covered by HMOs

Most HMOs provide comprehensive reproductive benefits. Although our survey did not examine reproductive benefits in indemnity or preferred provider organization plans, data from an Alan Guttmacher Institute survey show that HMOs are more likely than other types of plans to cover routine gynecologic care, reversible contraceptive services, and infertility services.[1]

Contraceptive services. Virtually all HMOs cover sterilization (either vasectomies or tubal ligations), although most do not cover the reversals of these surgical procedures (Table 1). About 90% of HMOs cover insertion or removal of intrauterine devices (IUDs), oral contraceptives, and diaphragm fitting. Of these, 78% provide for levonorgestrel implant (Norplant) insertion or removal, and 70% cover at least some diaphragm charges.

Provision of reversible contraceptive services is not associated with the size of the plan but is associated with HMO model type. Whereas 87% of group-model HMOs cover levonorgestrel implant insertion, 75% and 76% of networks and IPAs, respectively, cover this drug. Group models are also more likely to cover diaphragm prescriptions (83%) than the other model types. Group models are also the most likely to cover vasectomy reversals—17.2%, compared to 9.6% of IPAs and only 5.3% of network-model HMOs.

The term "coverage" does not mean that a service, device, drug, or procedure is done without any payment by the enrollee, however. Plans can provide a benefit and require enrollees to pay a deductible, copayment, or

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ABBREVIATIONS USED IN TEXT
GHAA = Group Health Association of America
HMO = health maintenance organization
IPA = independent provider association
IUD = intrauterine device

coinsurance. Few plans required a deductible to be paid for these benefits, and a coinsurance requirement was also uncommon. Copayments, however, were quite common. About three-quarters of the plans required some copayment for Pap tests, IUD insertion or removal, and diaphragm fitting; 67% for levonorgestrel implant insertion and removal; 58% for vasectomies; and 45% for tubal ligation. Average copayments for Pap tests were about $8, and copayments for IUD and levonorgestrel implant insertion averaged less than $10.

The use of copayments also varied considerably by HMO model type. Staff-model HMOs were the least likely to require copayments for any contraceptive service. For example, about 80% of group- and network-model HMOs required a copayment for IUD insertion or removal, but only 50% of staff-model HMOs had such a payment requirement. Group, network, and IPA models had similar percentages with a copayment for most of the contraceptive services listed, with a few exceptions. IPAs were less likely to have a copayment requirement for tubal ligation than the group or network models, and fewer group models (compared to networks or IPAs) had a copayment for levonorgestrel implant insertion.

Mammography, Pap tests, and abortion services. All HMOs surveyed covered mammography for women 50 years of age or older. Of group-model HMOs, for example, 17% do not routinely cover annual mammograms but provide them for high-risk women at the discretion of the physician or as often as mandated by state law.

Almost all HMOs (98%) also provide mammograms for women ages 40 to 50. For women between the ages of 35 and 40, however, HMOs do not routinely provide mammography, but instead usually provide a baseline mammogram unless the woman is at high risk or the physician orders one for another reason. Of group-model HMOs, 20% provide mammograms annually even to women between 35 and 40 years of age.

Although all HMOs cover Pap tests, as with mammography, the interval at which they may be provided varies. About 78% cover Pap tests annually and 18.5% cover them at the discretion of the provider "as needed" or less frequently than annually. IPAs are most likely to cover Pap tests annually, whereas group models are most likely to provide them at the discretion of the provider.

About 88% of HMOs cover at least some abortions. In our survey, 57% of HMOs responded that they cover abortions, and an additional 15% responded that "it depends." An additional 15% cover abortions only if they are medically necessary. Reasons for responding "it depends" included state prohibitions on certain types of abortion, coverage limited to only first-trimester abortions, and variations of the employer or specific plan. Some plans stated that they were owned by religious groups that did not condone abortion.

Abortion coverage also varied by HMO model type. Although 75% of staff-model HMOs covered abortion services with no restrictions, only 48% of IPAs did so. Networks and IPAs more frequently responded that it depends whether they provide abortions; no group-model HMOs gave this response, and only 4% of staff-model HMOs did so, compared to 21% of networks and 18% of IPAs. IPA models were also less likely to provide abortions under any circumstances. Of those responding, 19% of IPAs and 10% of networks did not provide any abortion services, compared to 7% of groups and 4% of staff-model HMOs.

Providers of Reproductive Services in Managed Care Organizations

Many women are concerned about their ability to choose their provider of gynecologic and obstetric ser-

TABLE 1.—*Contraceptive Benefits Offered by HMOs by Model Type, 1994*

Benefit	*All Plans (%)*	*Staff (%)*	*Group (%)*	*Network (%)*	*IPA (%)*
Intrauterine device	90.0	88.9	100.0	89.5	87.8
Diaphragm fitting	93.1	92.9	100.0	96.5	89.5
Norplant insertion	77.9	82.1	86.7	75.0	75.7
Norplant removal	79.2	82.1	90.0	75.0	77.4
Vasectomy	97.4	92.6	100.0	96.4	98.3
Vasectomy reversal	9.1	7.4	17.2	5.3	9.6
Tubal ligation	97.8	96.4	100.0	96.5	98.3
Tubal ligation reversal	7.0	11.1	13.8	3.5	6.1
Oral contraceptives	87.4	85.7	93.1	89.5	85.1
Depo-Provera	83.3	82.1	85.7	89.5	85.1
Diaphragm prescription	70.5	71.4	82.8	66.7	69.4

Source: GHAA Kaiser Family Foundation Survey of Reproductive Benefits, 1994
IPA = independent provider association
HMO = health maintenance organization

TABLE 2.—*Providers of Reproductive Services in HMOs, by HMO Model Type, 1994*

Benefit	*All Plans.(%)*	*Staff (%)*	*Group (%)*	*Network (%)*	*IPA (%)*
Member may select OB/GYN or self-refer	81.2	55.2	93.5	72.9	89.9
Member may select OB/GYN as personal physician	47.1	41.4	67.7	30.5	52.1
Member can self-refer to OB/GYN	70.2	50.0	80.6	66.1	75.4
Member needs new referral for each OB/GYN visit	20.1	10.3	3.3	30.4	21.4
Non-OB/GYN or MDs routinely provide OB/GYN care	91.2	96.6	100.0	89.7	88.1
Members may select nurse practitioner as primary provider of general care	16.9	53.6	32.3	19.3	3.4
Members may select CNM as primary provider of pregnancy-related services	38.7	14.3	16.5	23.1	46.2

Source: GHAA/Kaiser Family Foundation Survey of Reproductive Beneftis, 1994
CNM = certified nurse midwife
HMO = health maintenance organization
IPA = independent provider association
OB/GYN = obstetrician-gynecologist

vices. One HMO critic has charged that obstetrician-gynecologists have virtually disappeared as primary care physicians available to patients in northern California HMO markets and that HMOs severely limit the choice of reproductive health providers.[6] The data presented here shed new light on this situation.

Of HMOs surveyed, 81% either offer enrollees the choice of an obstetrician-gynecologist as their primary care provider or allow them to self-refer to one (Table 2). This is true for 55% of staff-model HMOs. Almost 94% of group-model HMOs allow enrollees either to choose an obstetrician-gynecologist as a primary care provider or to self-refer; 90% of IPAs and 73% of network-model HMOs do so. Group-model HMOs are also more likely to allow women to self-refer to an obstetrician-gynecologist (80.6%). Half of staff-model HMOs allow this.

Restrictions are sometimes placed on self-referrals, however. Although 70.2% of plans overall allow women to self-refer to an obstetrician-gynecologist other than their primary care provider, half of these plans limit visits to one per woman per year. Of HMOs that allow women to self-refer, 41.5% have no restrictions on the number of self-referred visits. About 9% have a limitation other than one self-referred visit per year. The most common other restrictions were allowing women to self-refer with no limits for obstetric (but not gynecologic) services; allowing self-referrals for well-woman examinations or annual Pap test and pelvic examinations; and other restrictions that varied by the individual IPA when more than one site or contract was included in the HMO.

Limitations on self-referrals varied substantially by model type. Of group and staff models that allow self-referral, 87% have no restrictions on the number of self-referred obstetric-gynecologic visits per year, compared to 28% of network and IPA models. Conversely, most network- and IPA-model HMOs that allow self-referral limit the number of self-referred visits to one a year (62%), whereas only 8% of group and staff models do so.[4]

Some restrictions on professional referrals also exist. Of those responding, 30% of networks and 21% of IPAs require a new referral for each visit to an obstetrician-gynecologist, whereas only 10% of staff and 3% of group models require this.

We asked which categories of nonobstetric-gynecologic providers routinely perform obstetric and gynecologic care. Virtually all HMOs responded that family or general practitioners routinely perform Pap tests (96%) and pelvic and breast examinations (97%). Only 60% of HMOs, however, responded that family or general practitioners routinely provide prenatal care for low-risk pregnancies, and only 52% said that these physicians deliver babies. This varies by HMO model type. In only 43% of staff-model HMOs did family or general practitioners provide prenatal care, although they did in 75% of networks. Family or general practitioners routinely perform breast and pelvic examinations in most HMOs (97%).

Certified nurse midwives are more often used to provide routine services in staff models (43%), although they routinely perform pelvic and breast examinations less often in IPAs (20%). Of all HMOs, 39% allow pregnant enrollees to select a nurse midwife to be the primary provider of pregnancy-related services. Whereas IPAs are less likely to allow nurse midwives to provide breast and pelvic examinations to nonpregnant women, however, almost half of IPAs (46%) allow members to select a nurse midwife as their primary provider of pregnancy-related services, compared to 14% of staff models.[7]

IPAs are also less likely to use physician assistants to provide breast or pelvic examinations than other types of

HMOs (26% compared to 75% in staff-model and 65% in group-model HMOs). IPAs are also the least likely of the model types to use nonphysicians to provide prenatal care, whereas staff models are the most likely to do so. For example, 50% of staff- and group-model HMOs routinely allow nurse practitioners to provide prenatal care, whereas only 15% of IPAs do so.

Contracts With Other Reproductive Health Providers

Although HMOs provide comprehensive reproductive health benefits, on average almost a fourth (23.3%) have contracts with family planning agencies such as Planned Parenthood to provide specific reproductive services. The service most often contracted out is abortion. Of HMOs, 14% reported that they contracted with family planning organizations only for abortions, whereas 6% contracted for abortion and other services.

More than 40% of staff-model HMOs contract out for any abortion services. IPA-model HMOs, on the other hand, were the least likely of the four HMO model types to contract with family planning organizations for any type of service; only 15% of IPAs had a contract with a family planning agency. More group-model HMOs had contracts with these organizations (primarily to provide abortions) than network-model HMOs (34.4% and 24.5%, respectively).

Plan size correlates with contracts with family planning agencies for reproductive services, primarily abortion. Of the largest plans (those with more than 122,000 members), 54% contracted out abortion services, compared to only 9% of the smallest plans (those with fewer than 30,000 members). Large plans are also more likely to cover abortions. Of plans with fewer than 30,000 enrollees, 65% cover any sort of abortion, compared with about 90% of plans with more than 122,000 enrollees. Larger plans may have reasons for offering abortion as a benefit but are unwilling to contract with a practitioner who provides abortions on a full-time basis.

Discussion

This survey documents that HMOs provide comprehensive reproductive health services. Although the exact extent of coverage varies by type of HMO, all types provide a broad range of contraceptive benefits and preventive services. Furthermore, the vast majority of HMOs allow women enrollees to either choose an obstetrician-gynecologist as their personal physician or to self-refer to one. Thus, most women HMO enrollees have easy access to obstetrician-gynecologists.

HMOs cover almost all reproductive services except vasectomy and tubal ligation reversals at a 70% to 80% level. Although these data are limited to HMO coverage, other data show that coverage for these services is more comprehensive in HMOs than in other types of plans. Mammography and Pap tests are covered at virtually the 100% level, but some plans allow them to be done at more frequent intervals than others. Similarly, most HMOs cover abortions under some circumstances, but many do not cover them unconditionally. In addition, most HMOs have modest copayments (averaging less than $10) for contraceptive services.

Although some HMOs have restrictions on the timing of mammography or Pap tests, such restrictions are consistent with published clinical practice guidelines. The American Cancer Society guidelines, for example, specify that screening mammography should begin by age 40 and women age 40 to 49 should have mammograms every 1 to 2 years, depending on physical and mammographic findings. Their guideline for Pap tests states that sexually active women and women age 18 or older should have annual Pap tests until three consecutive normal results are reported, after which the test may be done less frequently at the discretion of the physicians.[4]

As HMO enrollment rises rapidly, women and their families want to know how different types of providers, including HMOs, provide services of interest to them. Future research should be directed toward examining how reproductive services are provided in HMOs and in the fee-for-service sector. For example, although our survey documents the percentage of specific types of providers that provide selected reproductive services, we do not know which health care professionals are encouraged to provide these services by the HMO, nor the actual rates at which women receive these services by practitioner type. Future research should examine the effects of type of practitioner on utilization rates for specific procedures and the quality of the services provided.

More important, however, is research on the implications of coverage and practice patterns on the outcome of care. Such research should include examining whether restrictions on the number of self-referrals or professional referrals to obstetrician-gynecologists have any adverse effects on women, or whether the provision of coordinated primary care, including obstetric-gynecologic services, in managed care settings improves outcomes compared to less coordinated care settings.

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THE HENRY J. KAISER FAMILY FOUNDATION

Quality Assessment of Reproductive Health Services

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Systematic information on the quality of health services is being sought by purchasers and providers of health care. Consensus on an appropriate set of quality assessment criteria should stimulate the development of data collection tools and analytic methods. To begin the dialogue, criteria for evaluating the quality of family planning services, routine gynecologic care, infertility care, male reproductive health services, prenatal care, and early postnatal care are necessary. The effect of report cards on measurement and reporting and the challenges of assessing quality in family planning and other clinic settings are discussed.

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As purchasers of health insurance and health services continue to search for ways to reduce the cost of health care, providers will be increasingly pressured to demonstrate the value of the services they offer. Agreeing on a common set of methods for evaluating the quality of care will allow consumers to make informed choices and purchasers to evaluate health plan and provider performance.

For the purposes of this article, reproductive health services include family planning, routine gynecologic care, treatment for infertility, male reproductive health services, prenatal, and early postnatal care. The target population for reproductive health services is broad and includes most persons enrolled in health plans as well as the entire population using services at specialized clinics and in other service delivery settings. The potential providers of these services are primary care and specialty physicians and nonphysician health professionals.

Quality Assessment

Quality is defined by the Institute of Medicine as "the extent to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[1(p4)] Three separate but related activities constitute much of the current work on quality: practice guidelines, quality assessment, and quality improvement.

Practice guidelines have been developed principally to define appropriate processes of care for diagnosing and managing specific diseases or to outline schedules for providing certain preventive services. Guidelines are frequently developed through a professional consensus process, although recent efforts funded by the Agency for Health Care Policy and Research incorporate structured literature reviews as well.

Quality assessment activities determine the extent to which actual practice is consistent with a particular indicator of quality, such as adherence to a practice guideline. In most cases, operational definitions must be developed for components of the guidelines (such as defining levels of severity), and decision rules about what constitutes compliance versus noncompliance with a guideline element must be established (for example, if a screening test should be done at the first prenatal visit, will having it done at the second visit constitute noncompliance?). Thus, although quality assessment may be built on the algorithms provided in practice guidelines, an additional step is generally required to translate guidelines into quality indicators.

The purpose of quality improvement activities is to learn why failures to adhere to standards are occurring and to implement corrective action to bring practice into compliance. Most quality improvement activities are local, that is, the solutions to quality problems are unique to an individual health plan, clinic, or hospital. By contrast, in recent years, the development of national practice guidelines and quality assessment methods has been emphasized.

Quality assessment may be conducted for either internal or external audiences. For internal audiences, it is generally undertaken to stimulate quality improvement efforts. Some of the external audiences for quality assessments are accrediting organizations, purchasers or consumers of health services seeking comparative information, and groups wishing to contract for certain services (such as hospital care). The main focus of this article is on quality assessment undertaken for external audiences.

Although quality may be assessed at a variety of levels, the most common are at the health plan or clinic level and at the physician or other health professional level. This article focuses primarily on quality assessment at the health plan or clinic level; it is often difficult to conduct quality assessment at the level of individual providers because a provider may not have enough patients within any assessment category to allow for sta-

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ABBREVIATIONS USED IN TEXT

HEDIS = Health Plan Employer Data and Information Set
HIV = human immunodeficiency virus
NCQA = National Committee for Quality Assurance
STD = sexually transmitted disease

ble estimates of performance. Finding a reliable method for assessing the performance of individual providers is an important consideration for the future.

Overview of Quality Assessment Concepts and Data Sources

Building on a conceptual framework proposed by Donabedian,[2] three major aspects of care could be evaluated: the structure of the care delivery system, the process by which care is delivered, and the outcomes of care. Debate continues about the relative merits of evaluating each of these dimensions of care; to some extent, the purpose of the quality assessment (its focus on external versus internal uses) should determine which are appropriate to include.

The structure of the care delivery system includes a variety of community, individual, health provider, and health system characteristics that have been shown (or believed) to be associated with the likelihood of providing high-quality processes or outcomes of care. For example, the proportion of board-certified physicians in a health plan might be considered a structural indicator of the quality of care delivered by the health plan. Bed-to-population and provider-to-population ratios have been used as indicators of access to services. Until recently, most accreditation activity focused on structural measures such as these.

The process of care includes both technical and interpersonal dimensions and principally captures the content and method by which health providers deliver services to their patients. Most practice guidelines are designed to delineate the technical processes that constitute high-quality care. Evaluations of technical quality can examine both the appropriateness of service delivery (such as whether patients receive needed services and whether delivered services are necessary) and the skill with which services are delivered (for example, ensuring maximal effectiveness of the intervention). The interpersonal aspects of care have only recently been viewed as important, and assessments of providers' styles of interaction with patients are becoming more prominent. In general, the assessment of processes that have been linked to specific outcomes is preferred because the services are selected based on their demonstrated efficacy or effectiveness.

The outcomes of care include a multidimensional set of "results" from the delivery of services: clinical status, functional status, and satisfaction with care. Measuring outcomes as a method of quality assessment has grown in popularity over the past decade because conceptually, outcomes are the "bottom line" measure of the value of the health service product. The principal difficulty with using outcomes in external evaluations of quality is that many factors outside the control of the health care system, and particularly of the individual's current health plan, may influence outcomes. If one could account for those external influences and identify what portion of the observed outcome was directly affected by the quality of medical services, then outcome measures would be a powerful tool for quality assessment. Until adequate methods of severity adjustment and attribution of responsibility are developed, however, outcome measures should principally be used for research and internal quality assessment activities. The use of such measures for external audiences, particularly when the purpose is to compare health plans or providers, may misinform rather than inform and thus may not serve the intended objective of expanding the information available to make key decisions.

Three sources of data are generally used to conduct quality assessments: administrative data, medical records, and surveys. Administrative data can be broadly defined as those data that are systematically collected and maintained for a purpose other than quality assessment. Claim and encounter forms are the most common source of administrative data. Other sources are pharmacy records, health plan files on providers, and laboratory result systems. The principal advantages of administrative data are that they already exist and they provide information on the entire population using services. The principal disadvantages are that they lack clinical detail; inaccuracies may exist because the data are collected to pay claims rather than to evaluate quality; and information is available only on individuals who use services and file claims, complete encounter forms, or are included in one of the other data systems.

Medical record data are generally obtained by abstracting information from existing inpatient or outpatient records maintained by clinical personnel. The principal advantage of medical record data is that they contain substantial clinical detail about the technical processes of care and clinical status. The principal disadvantages are that they require a separate data collection process to be usable and that individual physicians vary in their patterns of recording information. For example, physicians taking a history commonly note only those areas in which the patient has a problem. A reviewer who is interested in the quality and comprehensiveness of history taking, however, must make assumptions about whether the absence of a note means that a question was asked and the patient had no clinically important response or that the question was never asked.

Survey data include information obtained by self-administered mailed questionnaires and telephone or face-to-face interviews with patients or providers. Survey data are necessary for obtaining patient assessments of the quality of interpersonal care, satisfaction with care, and many measures of functional status. Surveys may also be used to obtain provider attitudes and assessments of quality. The disadvantages of survey

TABLE 1.—*Illustrative Measures of Reproductive Health Quality by Conceptual Category and Data Source*

Data Source	Category of Quality		
	Structure	Process	Outcome
Administrative	Number of fertility specialists per 1,000 adult enrollees	Percent of women with a prenatal visit in the first trimester	--
Medical records	--	Percent of inappropriate hysterectomies	Rate of preventable neonatal deaths
Survey	Waiting time for a routine gynecologic appointment	Percent of teenagers reporting counseling from a health care professional about sexual activity	Patient satisfaction with the quality of family planning services

data are that a separate data collection activity is required and substantial variability in the methods by which surveys are implemented is likely, which in turn will affect the comparability or interpretability of the results. Making comparisons among health plans based on surveys conducted under different designs ranges from difficult to impossible.

Table 1 gives an example of quality indicators for reproductive health in each of the three categories—structure, process, and outcomes—that could be assessed using one of the three sources of data—administrative, medical records, and survey. It is rarely advisable to use administrative data for outcome measurement because data are generally not available to allow for adequate severity adjustment. An example of an outcome measure that could be derived from administrative data, and that is being used by some groups, is the proportion of low- or very-low-birth weight births occurring annually. Making such comparisons among plans is difficult because variations in these rates among health plans may be explained by differences in the populations served rather than by differences in the quality of care. In general, the medical record data are not an efficient or appropriate source of information for structural measures, so these are not illustrated.

Existing Reproductive Health Quality Measures

Various efforts are under way to provide external measures of the quality of care delivered in health plans, particularly in managed care. A measure is defined as the method by which an indicator of quality is scored. The measure includes the source of data, the variables to be included in the analysis, and the method by which the analysis is conducted. The word "measure" implies that the results are reproducible, either by other investigators using the same database or across databases, so that the numbers produced from a measure are comparable. Four efforts that are representative of different approaches are considered here:

- The Health Plan Employer Data and Information Set (HEDIS) was developed by the National Committee for Quality Assurance (NCQA) for use in comparing performance among managed care plans.
- Kaiser Permanente-Northern California Region has developed a quality report card that covers 100 performance measures.
- The RAND/HMO Quality of Care Consortium developed a measure that compares the quality of prenatal care provided in six managed care plans illustrates the use of a clinically detailed set of measures that rely on information abstracted from medical records to evaluate outpatient care delivered over a period of time.
- The RAND/HMO Quality of Care Consortium developed a measure of the appropriateness of the use of hysterectomy in managed care plans that illustrates the use of medical record data to evaluate the use of a specific intervention.

Taken together, these four efforts illustrate a range of options that might be considered in developing measures of the quality of reproductive health services, and they will facilitate a discussion of the different methods that can be used.

Health Plan Employer Data and Information Set

HEDIS (Version 2.0) provides detailed specifications for constructing measures of health plan performance in four areas: quality, access and patient satisfaction, membership and utilization, and finance.[3] Performance indicators were selected based on three criteria: the area was important to employers; health plans could feasibly provide data to construct the measures; and the information might facilitate improvements in the process of care.

A pilot project conducted in 21 health plans to test the feasibility, cost, and reliability of these measures was recently completed.[4] Although HEDIS contains guidance regarding standardizing some of the utilization rates by sex and age, in general the measures are not adjusted for differences in the populations enrolled in the participating health plans. Other caveats for potential users are provided in the HEDIS manual, including variations in the quality of health plan data, lack of comparability among health plans on many measures, the need for information on cost, and limitations on the use of these measures.

Despite these caveats, HEDIS measures have been widely adopted by employers, states, and other groups. The following results from the pilot study for indicators

related to reproductive health services illustrate the type of information available from this system. Overall results refer to the grand mean across all participating health plans, whereas the ranges refer to the results from individual health plans.

- Among women 21 to 64 years of age and continuously enrolled for the last three years, 77% received at least one Pap test in the past three years (range 54% to 89%).
- Among women who were continuously enrolled for the 12 months before delivery, 4% of births were classified as low birth weight (<2,500 grams); the range was from 0% to 8%. Results were not reported by health plan name because differences in the enrolled populations were not accounted for.
- Overall, 89% of pregnant women who were continuously enrolled for the 12 months before delivery began prenatal care in the first trimester (range 70% to 99%).
- The cesarean section rate was 19% overall (range 12% to 32%). The average hospital stay for an obstetric case was 2.32 days (range 1.7 to 3.1 days).
- The hysterectomy rate among women aged 15 to 44 years was 4.55 per 1,000 female enrollees, and the range was 1.8 to 10.42 per 1,000. For women aged 45 to 64 years, the hysterectomy rate was 8.14 per 1,000 female enrollees with a range from 3.6 to 16.0 per 1,000.

Indicators in the HEDIS system cover two of the categories of reproductive health services listed here—routine gynecologic services and prenatal care.

Kaiser Permanente-Northern California Region Quality Report Card

The Kaiser Permanente report card was intended for use by consumers and health care providers.[5] Each of the performance indicators is given and, where available, benchmarks are provided for comparison. A variety of data sources were used, including administrative data, medical record abstraction, linkage of membership information to other databases such as cancer registries and vital statistics records, and results of special studies conducted in the region. Simple graphics were used to show Kaiser performance compared to the benchmark, and a comparative column summarized the suggested conclusions. The report was divided into several categories: member satisfaction, childhood health, maternal care, cardiovascular disease, cancer, common surgical procedures, other adult health, and mental health and substance abuse. The following are some of the results of performance measures related to reproductive health services:

- Of pregnant women, 88% received prenatal care in the first trimester and 73% were screened for alpha-fetoprotein levels, 97% for hepatitis B, about 100% for syphilis, and 43% for the human immunodeficiency virus (HIV).
- About 6% of live births were categorized as low birth weight and 0.8% as very low birth weight; 0.5 per 1,000 live births had a neural tube defect, and 7.5% of newborns were classified as having a complex birth, such as requiring admission to a neonatal intensive care unit.
- The mortality rate in the hospital for low-birth-weight babies was 4%, and the perinatal mortality rate was 9 per 1,000 births.
- Of births, 16% were by cesarean delivery and 51% were vaginal after previous cesarean section.
- Among women aged 18 to 64 years who were continuously enrolled, 75% had had a Pap smear in the previous two years. Among those diagnosed with cervical cancer, 64% had local stage, 22% regional, and 6% distant. The cervical cancer mortality rate was 1.8 per 100,000 women.
- The hysterectomy rate was 444.5 per 100,000 women.
- In this survey, 87% of patients reported that they were satisfied or very satisfied with Kaiser. Among those who used obstetric services, 64% reported that obstetric care was very good or excellent.

Not surprisingly, given Kaiser's participation in the development of HEDIS, some overlap exists between the HEDIS measures and those provided in the Kaiser report card. Although the Kaiser report card provides considerably more information on outcomes, the comparability of the benchmark population is difficult to assess. For example, the benchmark information for the cervical cancer mortality rate comes from California Vital Statistics data, but no information is reported about the similarity between the population enrolled in Kaiser Permanente-Northern California and the state as a whole.

RAND/HMO Consortium—Quality of Prenatal Care

The HMO Quality of Care Consortium undertook a systematic process to identify clinical areas for the development of quality assessment measures for use in making comparisons among managed care plans.[6] The Consortium identified 14 clinical areas; prenatal care was one of the target areas for which a detailed clinical measure was developed and tested in six managed care plans.

A review of the literature combined with an expert panel consensus identified 48 processes of care for evaluating the quality of prenatal care.[7] A medical record abstraction instrument was developed to collect the information necessary to score compliance with each of the process criteria.[8] Although information was obtained on a variety of outcomes, such as birth weight, neonatal mortality, admission to a neonatal intensive care unit, premature delivery, and cesarean section rate, this information was not used for making comparisons among health plans. The process criteria were summarized in three scales—routine screening tests, other routine prenatal care, and condition-specific care. The first two scales consisted of criteria that applied to all pregnant women, so the score was a simple average of the per-

centage of those processes that were received by women in the health plan. The third scale principally captured follow-up care for women who had special problems during their pregnancies; the score for each woman was the number of processes received divided by the number of processes for which the woman was eligible.

The results demonstrated significant variations among health plans across all three scales.[9] Compliance among the health plans with the criteria for use of routine screening tests ranged from 64% to 93%. Compliance with criteria for provision of other routine prenatal care ranged from 78% to 87%, and compliance with care for specific conditions ranged from 54% to 77%.

This approach differs from those reviewed previously in that it provides considerable clinical detail from the medical record about the provision of one type of care; some elements of all three approaches are similar, however. Both HEDIS and Kaiser report on the proportion of women receiving their first prenatal care visit in the first trimester. This measure indicates whether the health plan had the opportunity to conduct a variety of other screening tests and interventions in a timely manner, but it does not indicate whether the full range of care was delivered. Kaiser also reports information on the use of screening tests for alpha-fetoprotein, hepatitis B, syphilis, and HIV. The Kaiser data do not indicate the time frame within which these screening procedures were conducted and the information was obtained from administrative data. An interesting question that remains to be explored is whether the results of a more detailed evaluation of the quality of the process of prenatal care would provide the same or different ranking among health plans as those resulting from the single-item measures.

RAND/HMO Consortium—Appropriateness of Hysterectomy

Another project of the HMO Quality of Care Consortium was assessing the appropriateness of the use of hysterectomy in seven managed care plans. Inappropriate use of hysterectomy, particularly among women who want to preserve the option of having children, directly affects the reproductive opportunities of the population. The scientific literature was reviewed to identify the reasons for performing hysterectomy as well as its efficacy and cost relative to other interventions. A comprehensive set of patient scenarios was developed, and a panel of physicians rated the appropriateness of hysterectomy for each scenario.[10] Patient medical records, including the two years of data on outpatient treatment before the surgical procedure, were reviewed to assess appropriateness.[11] Overall, 16% of hysterectomies were considered inappropriate, and the range among the individual health plans was 10% to 27%.[12]

Considering the appropriateness with which medical and surgical procedures are performed represents an alternative to reporting the rates at which such interventions are performed. In several studies conducted at RAND, no relationship has been found between the proportion of appropriate medical and surgical procedures and the rates of use.[13,14] From a quality perspective, appropriateness rather than utilization is the concept of interest. In the area of reproductive health, appropriateness assessments might be extended to the variety of interventions used to treat infertility. Because of the level of clinical detail required, information would have to be abstracted from medical records to assess appropriateness.

Summary

Although the measures considered above do not represent the entire spectrum of existing measures, they capture most of the existing content and types of measures. In terms of the range of reproductive health services that are currently being assessed, the principal focus has been on prenatal care and Pap tests. Little attention has been given to family planning, other aspects of maintaining reproductive health for men and women, and treatment of infertility.

Review of Other Standards

One source of standards for developing indicators of reproductive health services quality is *Healthy People 2000*.[15] This publication prepared by the US Public Health Service establishes health promotion and disease prevention objectives for the country. The objectives are organized around a number of topics: health promotion (including family planning), health protection, preventive services (including maternal and infant health), surveillance and data systems, age-related objectives, and special-population objectives. Within each topic area, objectives are grouped into three categories: health status, risk reduction, and services and protection. For this discussion of reproductive health services, the two areas that are most directly applicable for developing quality-of-care indicators are family planning and maternal and infant health.

Family Planning Objectives

Healthy People 2000 sets three health status objectives for family planning: reducing the incidence of teenage pregnancy, the proportion of unplanned pregnancies, and the prevalence of infertility. The suitability of these objectives for quality assessment criteria are considered below.

The report does not offer a clear-cut approach to the challenge of reducing the incidence of adolescent pregnancy. It indicates that programs will have to be tailored to local circumstances and that multiple factors influence an individual's decision to become sexually active. The most effective interventions are quite possibly outside the traditional health system—school-based programs, for example. Indeed, the emphasis of the related service and protection objective is on persons other than health professionals initiating discussions with adolescents about human sexuality. Thus, this area is probably not well suited to quality assessment at this time.

The proportion of unplanned pregnancies is one measure of the effectiveness of family planning services. The US Public Health Service defines an unplanned pregnancy as one that is either unwanted or mistimed and assesses the frequency of such events through self-reporting of respondents to an annual survey. The opportunities to provide information and guidance about the use of effective contraceptive agents extend across a broad range of health providers. Primary care physicians and specialists should be ensuring that their patients are familiar with and using appropriate methods of birth control according to their life circumstances, preferences, and other relevant factors. A large proportion of unplanned pregnancies (39%) occur among married women,[16] and the 20- to 24-year age group is at highest risk of having unplanned pregnancies.[17] Of unplanned pregnancies reported in the survey, 43% occurred among couples who were using a contraceptive method in the month of conception. The challenges are finding a reliable way to collect information on unintended pregnancies and controlling for factors external to the quality of health service delivery that affect these results.

Infertility results from various factors, but the most preventable cause is sexually transmitted diseases (STDs), particularly gonorrhea and chlamydia. Effective methods are available to screen for and treat gonorrhea; screening and treatment for chlamydia are somewhat less reliable. In addition to prevention, a variety of treatments are available for infertility, and measures related to the use of interventions that have been shown to be efficacious might be appropriate.

The risk reduction objectives related to adolescent sexual behavior include reducing the proportion of adolescents who are sexually active (currently and ever) and reducing unintended pregnancies among couples who are using contraception. The first group of objectives has some of the same problems discussed with respect to preventing adolescent pregnancy. Although effective interventions have been demonstrated, home environments and community values may be more important than interventions by health care professionals in affecting the decision about whether to engage in sexual activity. Thus, this represents a difficult area in which to develop quality measures. The other risk reduction objectives relate to the effective use of contraceptive methods, and these are more amenable to quality assessment because of the considerable body of knowledge that exists regarding efficacy.

The services and protection objectives involve increasing the proportion of adolescents who have had discussions about sexuality with a parent or parentally endorsed source; increasing the proportion of pregnancy counselors who offer accurate information about adoption; increasing the proportion of primary care professionals who provide age-appropriate preconception care and counseling; and enhancing the capacity of family planning and other clinics to provide the full range of services for STDs.

The standards related to knowledge levels among counselors (such as about adoption services) and primary care providers (for instance, regarding age-appropriate preconception care) and the service mix recommended for family planning clinics are reasonable inclusions in a quality monitoring system. The first services and protection objective focuses primarily on special programs related to religious or youth organizations that promote discussions about human sexuality. Although health care professionals can certainly play a role, the relative importance of this source of information is likely to differ across communities and populations within those communities. Indicators of quality related to the second and third objectives would assess the skill of health professionals (through surveys, for example), whereas the fourth objective suggests a structural indicator related to the availability of a spectrum of services for STDs at family planning and other clinics.

Maternal and Infant Health Objectives

Four health status objectives are provided in this area: reducing infant mortality rates, fetal death rates, maternal mortality, and the prevalence of fetal alcohol syndrome. One of the most important mechanisms for achieving all of these objectives is the provision of timely and appropriate prenatal care. Indicators of the quality of such services have been discussed and are recommended as a key dimension of quality assessment.

The risk reduction objectives include reducing the incidence of low- and very-low-birth weight births; increasing the proportion of pregnant women who achieve the minimum recommended weight gain during pregnancy; reducing the frequency of severe complications during pregnancy; reducing the cesarean delivery rate; increasing the proportion of women who breastfeed their babies; and increasing the proportion of women abstaining from the use of tobacco, alcohol, cocaine, and marijuana during pregnancy.

The first three objectives and the sixth are issues addressed during prenatal care visits, and they could be incorporated into measures that evaluate the quality of prenatal care. The cesarean delivery rate is reported in both the HEDIS and Kaiser systems, and lower rates are implied to be indicative of higher quality. A better approach would be to determine the appropriateness of the use of cesarean delivery. The US Public Health Service report points to factors outside of the direct service delivery system that determine the proportion of women who choose to breastfeed; the importance of external factors suggests this might not be an optimal criterion for assessing quality.

The services and protection objectives include increasing the proportion of women who obtain prenatal care in the first trimester; increasing the rate of screening for fetal abnormalities; ensuring that women receive care that is appropriate for their risk level (for example, high-risk women should deliver in a hospital with a

neonatologist on 24-hour call); increasing the proportion of newborns who are screened for genetic and other disorders; and increasing the provision of appropriate primary care services to children between birth and 18 months.

The first two objectives are included in the RAND measure of the quality of prenatal care. The third objective could be evaluated by examining the availability of facilities that are properly staffed for high-risk mothers and the presence of programs to match pregnant women to facilities with the appropriate level of care. The fourth objective includes both a screening component, which would be relatively easy to assess, and a treatment component that is likely to present some difficulties for making comparisons among health plans or clinics because of the small numbers of children with these problems. The final objective would require an assessment of the comprehensiveness and timing of well-child care; the frequency of such services is considerably easier to evaluate than the content of such care.

Potential Quality Indicators for Reproductive Health

The indicators shown in Table 2 are provided for the purpose of beginning to develop a comprehensive set of measures of the quality of reproductive health services. Within the context of a reporting system covering all aspects of health care, it is unlikely that measures for all of these indicators could be included, but they represent a reasonable starting point for evaluating the quality of care in this area. As measures are developed and tested, a more concise list of standards could probably be agreed upon.

The indicators proposed would require collecting information from the three sources of data discussed above—administrative, medical records, and surveys. Determining the best source of data will require an investigation of the reliability and validity of measures of these indicators using different data sources. Agreement on indicators will assist health plans, providers, and clinics in planning for future data and reporting systems.

Effect of Report Cards on Measurement and Reporting

In recent years, employers have been demanding more comprehensive information on the quality of the services they are purchasing, and health plans have been responding by developing various mechanisms for standard reporting of results. Thus, the expectation continues to grow that entities providing health services should measure and report on their performance.

The marginal cost of obtaining the necessary data will vary across organizations. Plans that use claim systems may already have the hardware and software in place to analyze claims to answer particular quality questions. Plans that do not use claims may have less extensive administrative databases related to the processes of care and may face considerable expense to purchase the necessary hardware and software. All plans have medical records, but access to those records varies depending upon the organization of the specific plan. Those with centralized inpatient and outpatient record systems have relatively easy access to records for quality assessment. Plans that contract with individual physicians may incur substantial time and expense obtaining photocopies of records for review purposes. Many plans currently conduct various surveys of patients and enrollees, although this is generally done to obtain information about satisfaction rather than other dimensions of quality.

Surveys often appear inexpensive relative to medical record abstraction or analysis of administrative data because the time to retrieve information is "contributed" by the respondent who is asked to fill out a questionnaire. The expense of conducting surveys increases when an organization endeavors to achieve high response rates—greater than 80%. Plans that routinely use surveys to obtain information may find that the marginal cost of adding to existing surveys or conducting new surveys is small, whereas plans that do not typically survey patients or enrollees may incur larger up-front costs.

Perhaps the most important point is that, if measurement and reporting become standard practices, incentives will be created to produce the necessary information at the lowest possible price. Thus, the critical consideration is what information is most useful for making comparisons among providers and for ultimately improving the quality of care delivered and, in turn, the health and well-being of the population.

Another concern that is frequently expressed is the response of health care providers to quality monitoring. One response is that providers will "play to the measures," that is, focus solely on delivering well those services that are being evaluated. If, as a result, other effective interventions or services are no longer provided or are done poorly, or if the areas being measured do not improve the health of the population, the health delivery system will be operating suboptimally. One approach that may mitigate "playing to the measures" is to have numerous potential quality assessment tools that are routinely and randomly rotated so that a provider is never certain which set will be applied in a given reporting period. Further, quality assessment should be focused only on those areas for which enhancing the quality of health services delivery will improve the health of the population.

The second type of response is "gaming" results (that is, taking actions to bias results by making them appear more favorable than would normally be the case). Performance measurement provides an incentive for health care providers to ensure that their results look as good as possible. Three mechanisms limit the potential for gaming results. First, some types of measures are more susceptible to gaming than others—for instance, opinion surveys may be influenced by the pool of

TABLE 2.—*Potential Indicators of the Quality of Reproductive Health Services*

Area	*Indicator**
Family planning	Number of qualified family planning providers per 1,000 enrollees (or provider-to-population-served ratios for clinics without an enrolled population) [S]
	Availability of screening, diagnosis, treatment, counseling, and provision of or referral to partner notification services for HIV infection and bacterial sexually transmitted diseases [S]
	Average length of time to obtain an appointment for family planning services [S]
	Proportion of health professionals who have accurate information about adoption opportunities (for patients with unintended pregnancies and those experiencing infertility) [P]
	Proportion of primary care physicians who have accurate knowledge about preconception planning and feel comfortable providing counseling in this area [P]
	Proportion of adolescents who indicate that they have talked to or would be willing to talk to a health professional in the plan or clinic about sexual practices and conception [P]
	Proportion of sexually active adolescents (younger than age 19) who are using combined-method contraception [O]
	Among those who have used services, satisfaction with the technical and interpersonal quality of family planning services [O]
Routine gynecologic services	Average length of time to obtain an appointment for a routine gynecologic examination [S]
	Percentage of women who have had a sexual history taken and a gynecologic examination performed in the previous three years [P]
	Percentage of women who have received a Pap test in the previous three years [P]
	Among those with a positive Pap test, proportion with adequate follow-up care [P]
	Proportion of sexually active women who have discussed contraceptive options with a health professional within the past five years [P]
	Percent of inappropriate hysterectomies performed in the past year [P]
	Satisfaction with the technical and interpersonal quality of routine gynecologic services [O]
	Distribution of stage at diagnosis for cervical cancer cases seen over the past two years [O]
Infertility care	Average length of time to obtain an appointment for evaluation of a fertility problem [S]
	Number of adequately trained fertility specialists per 1,000 population (or provider-to-treated population ratio for clinics) [S]
	Appropriateness of the use of infertility treatment alternatives [P]
	Among those using infertility treatment services, satisfaction with the technical and interpersonal care provided [P]
	Annual rate of sexually transmitted diseases per 100,000 population [O]
Male reproductive health	Percentage of men who have had a sexual history taken in the previous three years [P]
	Proportion of sexually active men who have discussed contraceptive options with a health professional within the past five years [P]
	Proportion of men who have ever had a clinical testicular examination [P]
	Proportion of men who have been instructed how to perform a testicular self-examination [P]
	Satisfaction with the technical and interpersonal care provided [P]
Prenatal care	Proportion of pregnant women who receive the following screening tests at the first prenatal visit: anemia, asymptomatic bacteriuria, syphilis, cervical gonorrhea, Rh factor and antibody [P]
	Proportion of pregnant women who receive the following tests before delivery: rubella immunity, screening for hepatitis B [P]
	Proportion of pregnant women whose first prenatal visit occurs in the first trimester [P]
	Proportion of pregnant women who had screening for alpha-fetoprotein levels (younger than age 35) or amniocentesis (age 35 or older) offered or received [P]
	Proportion of pregnant women for whom the symphysis-fundal height was measured at each visit between 20 and 32 weeks [P]
	Proportion of pregnant women whose blood pressure was measured at every visit [P]
	Proportion of high-risk pregnant women who received a one-hour, 50-gram glucose challenge test at 24-28 weeks [P]
	Satisfaction with prenatal care [O]
Early postnatal care	Adequacy of first well-baby visit [P]
	Proportion of low-birth-weight and very-low-birth-weight births occurring in an appropriately staffed facility [P]
	Proportion of newborns screened for genetic and other disorders [P]
	Rate of preventable in-hospital neonatal deaths [O]
	Among women with a delivery in the previous year, satisfaction with support provided in the hospital and immediately following discharge for newborn care [O]

*Indicators are categorized by whether or not they relate to the structure [S], process [P], or outcome [O] of care.

respondents that is selected—so attention should be given to selecting measures that are not subject to gaming. Second, for many measures of quality, an independent assessment team may be advisable. Accrediting organizations serve this function currently. Similarly, surveys could be conducted by a central group responsible for collecting and analyzing data for several organizations. This would ensure that consistent methods are used and that the group conducting assessments has no incentive to produce results that are not scientifically accurate. Third, an audit of results may be necessary. For example, measures that are constructed from reviews of medical records could be subjected to a reabstracting of a sample of records to compare whether the results were the same. NCQA included auditing in its pilot project and reported that this was an important strategy for ensuring the comparability and credibility of results.[4]

Challenges in Assessing Quality in Clinics

Many reproductive health services in this country are outside the traditional health care delivery system. Family planning and other clinics that provide specific services for a limited time or under a specific set of conditions are an important part of the health care system, and in the future they may be expected to produce reports on their performance. Because many of these clinics do not have an enrolled population for whom they are responsible, the use of population-based measures is not feasible. The most appropriate measurements of quality in these types of clinics will focus on the technical and interpersonal quality of the services that are provided. These measures will indicate how well care is delivered to those who seek it from that provider. Because many of these clinics may see patients who already have a preventable problem, measures of the prevalence of such problems would provide an unfair assessment of the quality of services provided.

Even with this restriction, however, some the measures recommended in Table 2 could be applied to the clinic setting to produce meaningful results. Measures related to the quality and knowledge of health professionals, access to care, satisfaction with care, response to specific interventions, and quality of the processes provided are examples of indicators that might be applied to such clinics. The challenges faced in measuring quality in specialized clinics are not dissimilar from those encountered in assessing the quality of indemnity plans. No link exists between these patients and a particular provider, and they may seek care from one provider for a preventable problem that was not addressed by another provider. Because it is not acceptable to measure quality for only a portion of the population—those enrolled in managed care plans—it is likely that measures will be developed and analytic tools refined that will facilitate assessment across all sectors of the health delivery system. Alternatively, the move toward managed care may eventually result in everyone having a link to a managed care system. Family planning and other specialty clinics may become part of larger health services networks. This provides a different solution—creating a population for whom the clinic is theoretically responsible.

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Standards of Care in Reproductive Health Services

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Standards of care for all medical services are designed by and for professionals and generally follow medical professional society guidelines. Most managed care organizations rely on professional medical standards of practice, which provide broad guidelines to providers. Family planning agencies, on the other hand, generally follow Title X program guidelines, which provide specific standards of care. The Title X guidelines include detailed instructions about service delivery and program content. The differences between these two sets of standards result in a wide variation in practice guidelines across the spectrum of health care providers. From the patient perspective, evaluation of care is generally not related to professional standards, but instead focuses on quality measures related to access and interpersonal aspects of care. The member satisfaction surveys developed by some managed care organizations now have a large enough sample size to provide meaningful measures of patient satisfaction at the individual provider level. A uniform set of practice guidelines is needed for family planning services that incorporates the strengths of all three approaches and that link performance to generally accepted practice guidelines.

(Barnes PW, Arpante NM, Lewis VC, Rosenfield A: Standards of care in reproductive health services. West J Med 1995; 163[suppl]:28-32)

Quality measures in health care have evolved from a focus on rigid structure and process to an evaluation of performance against criteria developed from generally accepted practice guidelines. Practice guidelines and medical standards are usually developed by professional organizations, such as the American Medical Association and specialty societies, and are designed to ensure the delivery of high-quality care. Practice guidelines allow for provider discretion, whereas medical standards are mandated practices.

At present, reproductive health services are evaluated in three ways:

• *Title X and Planned Parenthood Federation of America Family Planning Guidelines*: Title X of the Public Health Services Act defines the standards of care for family planning agencies that participate in federally funded programs. The purpose of Title X is to ensure the availability of specific services through a defined provider network, primarily family planning agencies. Because of the focused nature of the legislation and its efforts to widen the provider network beyond the traditional physician model, Title X contains detailed descriptions of standards of care and program content. The Planned Parenthood Federation of America (PPFA) is one of the largest providers of family planning services in the United States, and its *Manual of Medical Standards and Guidelines* is often used to define acceptable family planning practice.

• *Professional Practice Guidelines*: Family planning practice guidelines are included in the professional standards developed by the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). These standards and guidelines are not intended to define program or service content. Managed care organizations, in general, rely on professional medical association guidelines to define appropriate care.

• *Patient Perspective*: Standards of care for all medical services are designed by and for professionals and, generally, are not part of a patient's evaluation of providers. Although physicians emphasize high-quality care as a primary professional objective, most medical standards contain no specific definition of such care except the statement that quality assurance programs should be in place as one standard of care. Quality assurance programs generally assess whether the various standards of care are being met. In a hospital setting, such programs often focus on a particular procedure in more detail than do the general standards of care for that specialty.

The patient perspective, on the other hand, focuses on the availability of needed services and the acceptability of provider delivery. As a result, patient satisfaction surveys and report cards have been developed to provide information on service delivery factors such as waiting time and freedom of provider choice. Patients often assess quality of care by focusing on access and the interpersonal aspects of care.

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ABBREVIATIONS USED IN TEXT

AAFP = American Academy of Family Physicians
AAP = American Academy of Pediatricians
ACOG = American College of Obstetricians and Gynecologists
HIV = human immunodeficiency virus
MCO = managed care organization
PPFA = Planned Parenthood Federation of American
STD = sexually transmitted disease

A single, uniform set of guidelines is needed that combines the strengths of all three perspectives of evaluation and includes quality definitions and measures. The establishment of a single set of guidelines for family planning would provide the basis for quality measurement standards that can be used to assess performance and identify goals for practice improvements. These uniform guidelines should also define a standard benefit package for reproductive health services and readily available consumer information that patients can use to select a provider.

Comparison of Standards of Care

Most family planning agencies have developed practice guidelines based primarily on the Title X family planning guidelines. For this analysis, the PPFA *Manual of Medical Standards and Guidelines*[1] will be used to compare family planning agency standards to the medical society standards.

The PPFA manual provides specific instructions on program structure and patient services, including request forms and fact sheets that are used as screening and education tools. Emphasis is placed on age-specific counseling for all forms of contraception and preventive information, particularly regarding sexually transmitted diseases (STDs) and the human immunodeficiency virus (HIV). The medical profession guidelines are much less specific than those of the PPFA and allow broad discretion to providers. They also have a broader level of detail than that found in the PPFA manual.

Family planning agencies, particularly those receiving Title X funding, are required to provide a broad range of community education and outreach programs. Many PPFA affiliates, for example, have developed age-specific curricula that are used in agency programs or for teacher education. Agencies generally attempt to have some level of community involvement in the development and evaluation of these programs and to ensure cultural sensitivity that reflects community needs. Linkages are often developed between family planning agencies, school-based clinics, and other community providers in an effort to expand access to include a broader range of services.

Several large managed care organizations have developed wellness and health education programs that target specific groups, such as adolescents. Some plans, particularly those that enroll Medicaid recipients, have begun to implement community outreach projects, but these are generally part of marketing efforts. At present, few plans have developed links to community agencies other than health care providers.

The following analysis compares the practice guidelines defined by PPFA, ACOG, AAFP, and AAP with respect to four critical components of family planning services: contraceptive options, screening and testing for cancer and STDs, adolescent services and confidentiality, and continuity of care.[1-4] The PPFA standards represent practice guidelines used by family planning agencies, and the professional medical society guidelines represent the general practices of managed care organizations.

Contraceptive Options

The PPFA's standards include detailed discussions of contraceptive options, including oral and injectable contraceptives, implants, emergency hormonal contraception, intrauterine devices, and barrier and nonprescription methods such as fertility awareness. Each of these protocols contains a discussion of risks and contraindications as well as question and answer sheets for patients. Detailed discussion outlines are provided for all contraceptive methods, including periodic abstinence and fertility awareness.

Once a patient has chosen a method of contraception, an informed consent form is completed that includes the following instruction to the clinician: "The patient must receive a copy of the affiliate contraceptive methods brochure 'Facts About Birth Control' or its equivalent and must be given a copy of the FDA [Food and Drug Administration]-approved detailed patient labeling pamphlet, if any."[1(I-B-2.p1)]

Sterilization and abortion are fully discussed, again including patient-directed questions, information, and informed consent forms. With respect to abortion, options counseling addresses completion of pregnancy, adoption, and termination. Recovery room procedures include the direction that contraception must be discussed with each patient.

Both ACOG and AAP indicate that patients should be made aware of the availability, effectiveness, and relative risks of different methods of contraception, but the methods of delivering this information are not specifically enumerated. The AAP recommends including discussions of family planning during prenatal visits and visits with adolescents.

With respect to abortion, ACOG and AAP stress that abortion should not be viewed as a primary method of family planning. The American College of Obstetricians and Gynecologists indicates the need for options counseling, including adoption, abortion, and follow-up contraception after abortion. The American Academy of Pediatrics, focusing on adolescents, stresses the desire to review all alternatives for unwanted pregnancies but does not specifically enumerate the options. The American Academy of Family Practice focuses recommendations for contraceptive advice on adolescents, including the following:

AAFP is concerned about the incidence of adolescent pregnancy in this country. Abstinence, when practiced consistently, is identified as the most effective method of preventing unplanned pregnancy. Family physicians should provide counseling, including such techniques as building self esteem, to their adolescent patients to assist them in making decisions regarding abstinence. Minors should have access to medical consultation and the most effective contraceptive advice and methods, especially the role of abstinence, consistent with their physical and emotional needs.[4(p7)]

Specific contraceptive methods are not discussed.

Abortion is discussed in the context of a woman's legal right to make reproductive decisions and a physician's right to withdraw from a case involving abortion as long as it is consistent with good medical practice. Abortion counseling includes providing the patient with information on available financial and other assistance as well as prenatal services, adoption, and safe, legal abortion services.

Screening and Testing

The PPFA's standards discuss the importance of Pap tests for cancer screening and the use of colposcopy, cryotherapy, and the loop electrosurgical excision procedure as diagnostic tools. The importance of physician-conducted breast examinations and self-examinations are also stressed for cancer screening. Detailed instructions are given for treatment and referrals. In cases of notable findings, referrals are indicated.

The need for patient education and counseling is stressed throughout the protocols for STD and HIV screening, including descriptions of high-risk and safe sexual practices. For example, patient discussion guidelines include "Seven Steps to a Healthier and Safer Sex Life," which focuses on limiting the number of sexual partners, appropriate protection, and awareness of symptoms.[1]

The American College of Obstetricians and Gynecologists expands the discussion for screening procedures to include thyroid, abdomen, and rectal, in addition to pelvic and breast, examinations. Screening for STDs and HIV are not specifically outlined; however, these guidelines include the need to counsel patients concerning their sexual, psychological, and social needs.[2(p59)]

Adolescent Services and Confidentiality

The PPFA's guidelines indicate that patients will be served regardless of age, but they also stress the desire for parental involvement in the treatment of adolescents. The standards do not define specific protocols based on age. Confidentiality is specifically discussed with all patients as part of the counseling process, and a statement of a patient's right to confidential treatment, regardless of age, is included on the intake form.

The American College of Obstetricians and Gynecologists focuses special attention on reproductive services for adolescents, regardless of age, if they are sexually active; in addition, the organization indicates the need to ensure access to the most suitable methods of contraception. In the case of adolescent pregnancy, the guidelines encourage the involvement of partners and parents in options counseling. Both ACOG and AAFP have developed a joint statement stressing the need for confidentiality in adolescent health care.

Throughout its guidelines, AAFP makes specific references to the needs of adolescents. These include contraceptive advice (as indicated above), teenage pregnancy, and STD and HIV information. Physicians are directed to provide contraceptive advice and counseling on STDs "without being required to notify the minor's parents or guardians."[4(p8)]

Continuity of Care

Continuity of care is not addressed directly in standards of care. One of the important objectives of managed care, however, is to provide a higher level of coordination and continuity of care to avoid unnecessary treatment and duplication of services. In addition, quality and outcome measures can only be effective when a patient's medical care is understood as a whole.

The gatekeeper concept, used by most managed care organizations, is designed to strengthen continuity of care. As primary care physicians have become providers in managed care networks, they have begun to follow a reporting standard that results in centralized record keeping and a system of follow-up care designed to ensure patient access to needed services.

With respect to family planning agencies, many states have legislation that allows women covered by Medicaid to receive family planning services "out of network," without requiring prior approval by their primary care provider. Continuity of care may be less than desired because the family planning agencies are not necessarily integrated with other medical providers. In addition, because the scope of services of family planning agencies is narrowly defined, referrals for follow-up and treatment may not be closely monitored, creating the opportunity for repeated services or lack of treatment, or both. For example, the PPFA guidelines are specific with respect to what services should be referred to other providers, but no mechanism for follow-up exists to ensure that the patient has received the prescribed treatment.

At present, except within family planning agencies that have joined managed care networks, family planning patient records are not shared with other health care providers. This practice guarantees patient confidentiality but raises concerns about duplication of services and lack of follow-up.

Patients in managed care organizations are generally assured of a high level of continuity of care; however, most plans allow patients to go out of network, usually with some financial cost. These kinds of patient services are often not reported to the managed care organizations and incorporated into patients' records.

Patient Perspective

Patients who choose to receive family planning services through either a managed care organization or a

traditional family planning agency are faced with widely varying menus of services. Until patients walk in the door of a provider, however, they have little detailed information regarding the scope of services they can anticipate receiving.

The view is widely held that one reason why national health care reform did not succeed was the confusion about the effect the proposed changes would have on patients' ability to control the choices for their own health care. In the absence of national legislation, however, confusion is becoming increasingly widespread with respect to what standards are in place and what services are offered by various plans.

At present, the creation and presentation of managed care plans is being driven by cost competition. To borrow an analogy from industry, however, the power of the consumer usually becomes the dominant factor in determining which products are developed successfully.

In the 1970s, the automotive industry in the United States had more than 70% of the market share of cars sold in the US. It became apparent, however, that manufacturers did not understand the power of consumers to define value. In Japan, automobile makers developed a well-engineered, fuel-efficient car, which was what consumers said they wanted. As a result, over the next 20 years, the US automotive industry market share dropped to 30% in spite of pricing discount programs.[5]

Clearly, health care is not automobile manufacturing. The purpose of this analogy is to emphasize the inevitable need to focus on the patient in the design of medical care delivery models.

Recommendations and Conclusions

An effort should be made to create a uniform set of guidelines for family planning on a national level. These guidelines should include professional guidelines and quality measures that can be used by consumers to evaluate and choose providers. An industry board should be created for this purpose, consisting of providers that represent the appropriate specialties, representatives of managed care organizations, and family planning agencies. Most importantly, this board must include consumer representatives.

The practice guidelines should define a basic service package for family planning services and should include the following components:

- All major reversible and permanent methods of contraception should be available.
- Patient counseling and information should be a mandatory component of any program and should include age-specific guidelines for adolescents.
- Counseling regarding pregnancy options, including abortion, should be clearly defined in all programs with appropriate referrals and follow-up care.
- Where abortion services are provided, contraception counseling and services should be available as well.
- Education, testing, and integrated follow-up care for STDs and HIV must be included in any minimum benefit package. Although parents and schools should provide the most basic level of sexuality education, health care professionals should not assume that patients have an adequate understanding of the risks associated with sexual activity.
- Population-based outcome measures should be defined and published for all providers, including rates of unintended pregnancy, teen pregnancy, abortion, and STD and HIV infection.

Reproductive health care that follows defined practice guidelines can lead to meaningful performance assessment and goals for practice improvement.

Managed care organizations provide the greatest promise for continuity of care through implementation of the primary care model. Family planning agencies, which bring to the health care arena a particular depth of counseling, education, and outreach services, should be incorporated into managed care organizations and presented as an integrated choice to plan participants. In addition, family planning agencies should attempt to broaden services to provide a greater continuity of care and follow-up.

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APPENDIX
Summary of Program Guidelines

Required Services

Client Education/Counseling

- information about all methods
- age appropriate
- informed consent for each contraceptive method, including discussion of safety, effectiveness, side effects, complications, and danger signs
- planned return schedule or appointment
- 24-hour telephone access and emergency location
- special counseling (such as preconception, pregnancy management, sterilization, genetic, nutritional, sexual)

Fertility Regulation: must make available, directly or through referral, all methods of contraception approved by the California Department of Health and Human Services:

Temporary
- barrier methods (female and male)
- intrauterine devices (IUDs)
- fertility awareness and natural family planning
- hormonal contraceptives

Permanent
- sterilization (female and male)

Emergency contraception for unexpected mid-cycle intercourse
- Yuzpe regimen: although not approved by the Food and Drug Administration, widely used in the United States, replacing DES as the method of choice (an alternative is the insertion of a copper-bearing device within 72 hours of intercourse)
- birth control counseling to discourage use of emergency contraception as routine method

Pregnancy Diagnosis and Counseling

- nondirective counseling on pregnancy issues
- prenatal care and delivery
- infant care, foster care, and adoption
- pregnancy termination

Adolescent Services

- skilled counseling and detailed information
- appointments available on short notice
- discussions on abstinence
- confidentiality and encouragement of parent/family discussion
- information about all methods of contraception, if contraception is requested
- testing for sexually transmitted diseases (STDs) encouraged for high-risk teens

Sexually Transmitted Diseases

- gonorrhea culture for IUD insertion or high-risk patients
- collection of patient and partner information, screening, and testing for all common STDs and for human immunodeficiency virus

Legal Issues

Nondiscrimination: *services provided without regard to religion, race, color, national origin, creed, handicap, sex, number of pregnancies, marital status, age, and contraceptive preference*

Confidentiality: *provide safeguards against invasion of personal privacy*

Community Participation

Review of informational and educational materials by community representative of advisory committee
Participation in development, implementation, and evaluation of service providers
Ensurance of availability of culturally appropriate materials and services
Provision of community education in family planning, values clarification, family life, and human sexuality

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From Program Guidelines for Project Grants for Family Planning Services.[6]

THE HENRY J. KAISER FAMILY FOUNDATION

Beyond the Freedom to Choose

Medicaid, Managed Care, and Family Planning

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In this article we examine the federal freedom-of-choice statute, which was enacted in the mid-1980s to protect Medicaid beneficiaries' access to timely and confidential family planning services. We also examine how these provisions have been implemented in 15 jurisdictions and provide a case study of 5 family planning programs. We found that this attempt to "carve out" family planning services from managed care has led to numerous problems. First, there is virtually no federal guidance concerning to which services and supplies the exemption applies. Second, there are no guidelines as to how carve-outs are to function. Therefore, if managed care systems are inaccessible or nonresponsive to reasonable community care seeking patterns, then a carve-out may be the only answer. Carve-outs should be used as a last resort, however, because they are so difficult to design.

(Rosenbaum S, Shin P, Mauskopf A, Fund K, Stern G, Zuvekas A: Beyond the freedom to choose—Medicaid, managed care, and family planning. West J Med 1995; 163[suppl]:33-38)

Federal legislation enacted in the mid-1980s exempted family planning services from restrictions on the ability of Medicaid managed care enrollees to select their own health care provider. The freedom-of-choice statute was enacted to protect access to timely and confidential family planning services and to aid family planning providers without managed care contracts. These were chiefly publicly funded clinics located in low-income and underserved areas, which have long been a source of high-quality family planning to poor women.

The legislation also raised new and difficult questions that are probably inherent in any effort to "carve out" from managed care contractual arrangements certain covered health services. The difficulties that have arisen in the implementation of the family planning freedom-of-choice exemption are emblematic of the problems that surface when policy makers attempt to deal with the shortcomings of managed care's structure by trying to avoid them altogether rather than by modifying the system to meet important patient needs.

The problems caused by service "carve-outs" potentially affect the accessibility and quality of comprehensive health care for managed care enrollees. Moreover, the family planning freedom-of-choice exemption ironically may have harmed the same professionals whom it was intended to assist. By simply sparing certain types of services and health care professionals from managed care network arrangements rather than providing for their integration, the freedom-of-choice exemption effectively has isolated public family planning programs during a critical period in the growth of Medicaid managed care.

Now that the problems for both patients and providers caused by this carve-out have become clearer, many family planning programs are finding that they lack the skills and capabilities to attempt the integration approach. In effect, these health care professionals, as well as many managed care plans, have lost a decade of adaptation. The law excused the principal stakeholders in the system—providers, plans, and state Medicaid agencies—from the hard task of making the necessary accommodations to meet patients' needs for confidential services from health care professionals and in settings that patients know and trust.

This study has implications for a wide range of specialized primary and referral services ranging from preventive interventions to promote patients' health to specialty care for children and adults with multiple disabilities. All of these programs and providers are affected by the development of managed care plans, yet simply exempting these entities from managed care may produce similarly troubling results. Thus, although this study examines "carve-outs" under Medicaid managed care systems, its findings are of direct relevance to any effort to broaden the scope of managed care.

Issues in Implementing the Family Planning Exemption

The degree to which the family planning exemption statute has been able to achieve its objectives turns on three separate but related matters:

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ABBREVIATIONS USED IN TEXT

FFP = federal financial participation
HCFA = Health Care Financing Administration
HMO = health maintenance organization
PCCM = primary care case management
STD = sexually transmitted disease

- The degree to which the definition of exempt "family planning" services actually encompass all of the family planning items and services that patients might seek on a confidential basis;
- The degree to which the exemption applies to all potential managed care arrangements;
- Whether the Health Care Financing Administration (HCFA) and state agencies have implemented the exemption in a manner consistent with the best interests of patients to ensure access to timely, confidential, and comprehensive family planning services.

The Ambiguity of the Definition

Regulations promulgated by HCFA (the federal agency that administers Medicaid) lack any definition of family planning services, as the term is used in the statute granting the freedom-of-choice exemption. The only HCFA definition is found in the rule that describes a more limited set of family planning services that qualify for a higher rate of federal financial participation (FFP) of 90% reimbursement for every state dollar spent. The lack of a regulatory definition of family planning, other than the partial definition contained in the FFP rule, creates serious problems because there is virtually no federal guidance as to which services and supplies fall under the exemption. If state managed care systems use the limited "enhanced FFP" standard rather than the broader medical assistance definition to define the scope of the freedom-of-choice exemption, important family planning services may not be available on a free-choice basis.

Of particular importance is that treatment for sexually transmitted diseases (STDs), although clearly a family planning service, does not appear in the FFP rule. Although a primary reason for seeking confidential family planning services is treatment of STDs, use of the FFP standard to determine the scope of the freedom-of-choice exemption would leave this treatment outside the scope of the exemption. Managed care enrollees would be unable to obtain insured STD treatment services on a free-choice basis, although the examination and diagnostic services necessary to detect the presence of an STD would be covered.

Limited Application of the Exemption

Notably, the freedom-of-choice exemption does not apply to managed care research and demonstrations carried out under Section 1115 of the Social Security Act (Table 1). Instead, it covers only voluntary managed care arrangements (which are practically nonexistent today) and mandatory managed care systems operating under Section 1915 of the act. Currently, 14 states are either operating managed care systems under Section 1115 or have sought waivers under Section 1115 to institute statewide mandatory managed care demonstrations. Several Section 1115 states already honor or intend to honor the freedom-of-choice exemption, although there is no requirement that they do so. As many as 20 more states may apply for Section 1115 demonstration authority.[1]

No Federal Implementation Standards

There are virtually no federal standards to guide states in implementing the statute. There are no federal regulations regarding certain practices by plans such as previous gatekeeper approval before out-of-network care can be obtained. Nor are there federal standards for direct state or plan payments to non-network family planning providers; confidentiality-of-care rules; or standards governing plan treatment of family planning providers' follow-up care requests made on patients' behalf in the case of nonexempt services that enrollees must obtain through their gatekeepers (such as pregnancy or STD treatment following assessment and diagnosis).

State Implementation of the Freedom-of-Choice Exemption

As indicated earlier, there is almost limitless potential for state-level variation in implementation of the freedom-of-choice requirements. First, there is no uniform federal definition of what constitutes a protected family planning medical assistance service, even though the freedom-of-choice statute hinges on such a definition. Second, the freedom-of-choice provisions do not apply in states operating their managed care systems under Section 1115 waivers because the free-choice-of-provider requirement is waived. For example, the state of Massachusetts, in its Section 1115 application, specifically sought a family planning free-choice waiver only for persons enrolled in full-risk plans such as those offered by health maintenance organizations (HMOs).

Tables 2, 3, and 4 show the pattern of variation in the implementation of the Medicaid freedom-of-choice provisions in 15 jurisdictions, selected in accordance with a

TABLE 1.—*Applicability of Family Planning Freedom-of-Choice Rules to Medicaid Managed Care Arrangements by Statutory Basis of Managed Care System*

Arrangement	*Freedom of Choice for Family Planning*
Voluntary enrollment in a federally qualified HMO or HIO under §1902 (a)(23) of the Social Security Act	Yes
HHS freedom of choice waivers under §1915(b) of the Social Security Act	Yes
HHS demonstration waivers under §1115 of the Social Security Act	No

HMO = health maintenance organization, HHS = health and human services, HIO = health insuring organization

TABLE 2.—*Organizational and Statutory Characteristics of Survey of State Managed Care Plans and Contracts*

State	*Plan Type*	*Inclusion of Family Planning a Required Contract Service*	*Statutory Basis of Operation*
Arizona	Fully capitated	Optional with health plan	§1115
District of Columbia	PCCM	No	§1915(b)
	Fully capitated	No	§1915(b)
	Fully capitated	No	Voluntary
Florida	PCCM	No	§1915(b)
	Fully capitated	Optional with health plan	Voluntary
Illinois	PCCM	No	§1915(b)
	PCCM/physician network	No	§1915(b)
	Fully capitated	Yes	Voluntary
Kentucky	PCCM	No	§1115
	Fully capitated	No	§1115
	Partially capitated	No	§1115
Maryland	PCCM	No	§1915(b)
	Fully capitated	Yes	Voluntary
Michigan	PCCM	No	§1915(b)
	Partially capitated	Yes	§1915(b)
	Fully capitated	Yes	§1915(b)
Minnesota	Fully capitated	Yes	§1915(b)
	Fully capitated	Yes	Voluntary
New Hampshire	Fully capitated	Yes	§1115
New Mexico	PCCM	No	§1915(b)
	PCCM	No	§1915(a)[2]
North Carolina	PCCM	No	§1915(b)
	Fully capitated	Yes	Voluntary
Oregon	PCCM	No	§1115
	Fully capitated	Yes	§1115
Pennsylvania	HIO	Yes	§1915(b)
	Fully capitated	Yes	Voluntary
Rhode Island	Fully capitated	Yes	§1115
Utah	PCCM	No	§1915(b)
	Fully capitated	Yes	§1915(b)
	Partially capitated	Yes	§1915(b)

PCCM = primary care case management, HIO = health insuring organization

variety of demographic and managed care organizational factors—population size and mix, geographic location, the extent to which managed care plans are in use, and the types of managed care plan arrangements used. The information used to carry out this part of the study comes from numerous sources, including state program regulations and guidelines, provider manuals, managed-care contracts and accompanying instructional materials, and other relevant official documents.

Table 2 shows the range of managed care arrangements in effect at the study sites. There are three basic financial structures permitted under states' managed care programs[2]:

• *Full-risk plans*: Full-risk plans maintain written contractual agreements with their participating providers and may pay them on a fee-for-service or subcapitation basis. Full-risk plans operate at a financial risk for the cost of outpatient and inpatient care and services that are included in the contract. Full-risk plans may be federally qualified HMOs, state-certified HMOs, or HMOs operating under Section 1115 waivers of federal and state requirements.

• *Partial-risk plans*: Partially capitated plans (known under federal guidelines as prepaid health plans or PHPs) function much like full-risk plans. Participating providers are at financial risk for one or two categories of outpatient Medicaid services and may assume case management and gatekeeping functions for other covered services not included in the capitation rate.[3]

• *Primary care case management (PCCM) systems*: Under a PCCM system, enrollees select a primary care provider from whom they obtain all "primary" health care services. The provider is directly under contract to the Medicaid agency and provides care on a fee-for-service basis. Of the more than 8 million persons enrolled in Medicaid managed care in 1994, most were enrolled in either full- or partial-risk plans.

In the case of PCCM networks (that is, a primary care physician or provider who furnishes basic medical

care and performs case management functions), the surveyed states uniformly do not require contractors to provide family planning services as an in-office primary care service (Table 2). In the case of partially and fully capitated plans, however, states are divided on the question of whether family planning services are a required contract service. Because family planning services are a capitated contract service in most of the study states, patients would be required to obtain family planning services through their plans' provider networks (either directly from their gatekeeper or through referral to another network provider) in the absence of the freedom-of-choice provision. This tendency to capitate family planning—a common service in many private HMOs—is an indication that states and plans consider the service as amenable to risk capitation payment as well as to managed care gatekeeping.

The study states vary notably in the extent to which key types of family planning services are exempt from the freedom-of-choice requirements (Table 3). Generally, managed care enrollees in the study states are not granted free choice of provider for such important family planning services as treatment of STDs or other conditions that may directly affect the timing of pregnancy and spacing of children.

The study states prefer to leave to health plans the decision as to how enrollees' family planning preferences will be honored (Table 4). States do not require plans to extend full "in-network" provider status to all family planning providers as a means of carrying out the freedom-of-choice requirement. Indeed, states appear willing to make double payments to independent family planning providers to ensure unrestricted access to these services rather than mandate contractual relationships. As the national health reform debate over treatment of certain "essential community providers" has underscored, mandatory contracting requirements are viewed as controversial, particularly if primary gatekeepers ("full-practice" primary care providers such as family practice physicians, community health centers, and rural health clinics) are at financial risk for the care. In these states, the freedom-of-choice exemption is honored either through direct state payment to nonparticipating providers for care furnished to enrollees (a double payment is made, for instance) or through rules requiring plans to pay nonparticipating family planning providers out of their monthly capitation.

Numerous states require previous authorization for family planning services, even though this practice raises serious issues concerning patient confidentiality and thus appears to conflict directly with the freedom-of-choice requirements (Table 4). Previous authorization also can be expected to increase the likelihood of "out-of-plan" (unauthorized) use of family planning services by enrollees unwilling to seek permission to use care;

TABLE 3.—*State Medicaid Classification of Family Planning Services*

State	Counseling and Patient Education	Exams and Treatment	Labaratary Tests*	Treatment of STDs	Cantraceptive Devices and Supplies	Infertility Services	Hysterectamy	Maternity Care	Treatment of Other Canditians Affecting Repra-ductive Health	Abartian
Arizona	Y	Y	Y	N	Y	N	N	N	N	N
District of Columbia	Y	Y	Y	N	Y	Y†	N	N	N	Y
Florida	Y	Y	Y	N	Y	N	N	N	N	N
Illinois	Y	Y	Y	N	Y	Y	N	N	N	Y
Kentucky	Y	Y	Y	vaginal secretions only	Y	Y	N	pregnancy testing only	vaginal secretions only	N
Maryland	Y	Y	Y	N	Y	Y	N	N	N	N
Minnesota	Y	Y	Y	N	Y	Y†	N	N	N	N
New Hampshire	Y	Y	Y	N	Y	Y	N	N	N	N
New Mexico	Y	Y	Y	N	Y	Y†	N	N	N	N
North Carolina	Y	Y	Y	N	Y	Y†	N	N	N	N
Oregon	Y	Y	Y	N	Y‡	Y†	N	N	N	N
Pennsylvania	Y	Y	Y	N	Y	Y	N	N	N	N
Rhode Island	Y	Y	Y	N	Y	Y§	N	N	N	Y
Utah	Y	Y	Y	N	Y	Y†	N	pregnancy testing only	N	Y

STD = sexually transmitted disease, Y = yes, N = no

*Including tests for STD, HIV, pregnancy testing, and pap smear.
†Voluntary sterilization only.
‡Prescribed drugs and devices only.
§Voluntary sterilization, infertility treatment limited to married enrollees.

TABLE 4.—*State Implementation of Freedom-of-Choice Provisions in Capitated Plans and Prior Authorization*

State	Managed Care Plan	Inclusion of Family Planning Services in Capitation Contract	Family Planning Provider Inclusion Required	Payment Made by Plan to Non-network Family Planning Provider	Payment Made by Plan to Network Family Planning Provider	Prior Authorization Required
Arizona	AHCCS (full risk)	Plan option	No	Yes*	Yes†	Yes‡
District of Columbia	DC Managed Care (full risk)	No	No	--	Yes	--
	Chartered Health Plan (full risk)	No	No	--	Yes	Yes
Florida	Prepaid Health (full risk)	No	No	Yes*	Yes†	--
Illinois	Prepaid Health (full risk)	Plan option	No	--	Yes	Yes
Maryland	HMOs (full risk)	Yes	No	Yes	--	--
Michigan	Clinic Plan (limited risk)	Yes	No	--	Yes	--
	HMO (full risk)	Yes	No	--	Yes	--
Minnesota	Prepaid Medical Assistance Program (full risk)	Yes	Yes	Yes§	--	--
New Hampshire	HMO (full risk)	Yes	No	--	Yes	--
North Carolina	HMO (full risk)	Yes	--	Yes	--	--
Oregon	Oregon Health Plan (full risk)	Yes	No	--	Yes	--
Pennsylvania	HealthPASS (full risk)	Yes	No	Yes	--	--
	HMO (full risk)	Yes	No	--	--	--
Rhode Island	RIte Care (full risk)	Yes	No	--	--	NA‖
	HMO (full risk)	Yes	No	--	--	--
Utah	Choice of Health Care Delivery Program (limited and full risk)	Yes	No	--	Yes	--

HMO = health maintanence organization

*if included in contract.
†if not included in contract.
‡Only if family planning is included as a contract service.
§1994 Legislature requires plans to contract with certain providers. The legislation is now in the process of being implemented.
‖Out-of-plan family planning providers are not reimbursed for services they provide to managed care enrollees.

such authorization requirements will thereby result in unreimbursed services as well.

Profiles of Family Planning Programs in Medicaid Managed Care

The following profiles of providers in five of the study states (Michigan, Illinois, Florida, Minnesota, and Pennsylvania) illustrate the different approaches these states have taken in implementing the freedom-of-choice requirements and the different ways in which health plans and family planning providers have responded to the exemption.

In Michigan, where the state pays family planning providers directly for care furnished to managed care plan enrollees, non-network family planning programs have difficulties in making referrals for covered services they do not offer. Moreover, they have not developed relationships with patients' health plans or resolved ways to ensure continuity of care while preserving patient confidentiality. In Michigan, the direct payment system appears to work well.

Like Michigan, Illinois provides for direct payment to family planning providers serving women enrolled in capitated managed care plans. The situation for providers in this state is far different, however, because the state's mechanism for payment is substantially more complicated. As a result, family planning providers that treat patients enrolled in HMO-type plans report lengthy payment delays and are increasingly unwilling to accommodate out-of-plan Medicaid managed care enrollees in their practices.

In Florida, non-network family planning providers are required to submit claims for services to the HMOs in which the patients are enrolled. Of all the states studied, the Florida system appears to present the most serious problems, with thousands of dollars of unpaid claims outstanding and the continued existence of at least one heavily used public family planning program seriously threatened by the high volume of uncompensated ambulatory care.

The case of Minnesota illustrates the consequences of an environment in which the use of HMOs is widespread, ultimately leading to state legislation regulating the terms of provider access to managed care network status. In the past, access to family planning services

was limited on an "in-network" basis. Both publicly and privately insured women made heavy use of non-network providers that, in turn, could not get paid. These factors contributed to passage of a law requiring all network-style managed care plans to contract with all family planning providers in their service areas.[1] The state operates its managed care system under Section 1115 waivers and therefore is exempt from the freedom-of-choice requirement.

Of all of the programs reviewed, that of Pennsylvania provides the only example in which the freedom-of-choice requirement served as a springboard for integrating family planning providers into managed care. Drawing upon well-organized systems that predated the introduction of Medicaid managed care and with substantial foresight, family planning providers in both Philadelphia and Pittsburgh have been able to maneuver through the evolving web of managed care to become active participants in health plans, even without regulatory protections. The fact that the Pennsylvania experience appears to be so unusual is indicative, perhaps, of the degree to which the freedom-of-choice exemption has slowed change as well as the limits of voluntary collaboration between managed care organizations and publicly funded providers of specialized primary health services in the absence of formal requirements.

Conclusion

Our study illustrates the consequences of a policy decision to exempt one class of services from managed care arrangements to aid both patients and (in this case, predominantly publicly assisted) providers. First is the problem of identifying with clarity the items and services that are to be subject to the exemption. HCFA's failure to define the scope of the family planning freedom-of-choice statute has had a serious effect on the reach of the exemption, particularly in the case of treatment for STDs. Every category of services, whether family planning, pregnancy-related care, or services for children with special needs, suffers from this type of ambiguity. Without a clear definition of which services are exempt, the exemptions may provide little relief from the fundamental problems for which the exemption is sought.

The second problem is the failure to provide clear and consistent guidance regarding how a "carve-out" arrangement is to function. In the case of family planning, these functional problems include previous authorization, provider payment, the management of treatment referrals from non-network providers, and patient confidentiality. The lack of HCFA regulations in these areas has led states to create their own systems, which vary in terms of the services exempted, the provider relationships required, and the details of provider payment systems.

The challenge of making health care accessible does not disappear simply because a person enrolls in a managed care plan and is assigned to a gatekeeper. Indeed, the task of creating accessible health services begins when enrollment occurs. If managed care systems are inaccessible or nonresponsive to reasonable community care-seeking patterns, then a "carve-out" may be the only answer. But because these arrangements are so difficult to design properly, they should be used as a last resort rather than as a first strategy. A better strategy is to integrate into managed care systems the already-existing providers who form the health care backbone in underserved communities. These providers must be given the financial and technical resources needed to achieve integration, as well as the continued grant support they need to furnish care to uninsured patients and to provide essential health and supportive services that are not covered. If integration cannot be achieved voluntarily, then health plans should be required to accommodate the inclusion of these providers if they wish to do business in underserved communities.

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THE HENRY J. KAISER FAMILY FOUNDATION

Case Studies of Collaboration Between Family Planning Agencies and Managed Care Organizations

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To learn more about collaboration between family planning agencies and managed care plans, telephone interviews were conducted with staff at ten sites across the country, including offices of Planned Parenthood and other agencies. These examples of collaboration indicate that the development of each partnership is influenced by contextual factors such as the penetration of managed care into the local market, the patient profile of the clinics, government regulations, and the political environment. Although establishing relationships with family planning agencies is often not a high priority for the health plan organizations, they prefer to deal with networks of providers when the need for a family planning referral arises. Family planning agencies are increasingly moving toward expansion of services into primary care to make themselves more attractive to managed care plans. Developing strategies for sharing information while maintaining patient confidentiality represents an important challenge to family planning agencies as they move toward integration with managed care plans. Family planning providers also face obstacles because they are not usually organized to handle the complex financial and contractual issues that come with collaboration.

(Orbovich C: Case studies of collaboration between family planning agencies and managed care organizations. West J Med 1995; 163[suppl]:39-44)

This article documents the experiences of several family planning agencies that have recently negotiated contracts with managed care networks or are in the process of developing a more formal relationship with managed care plans. Background interviews were conducted with ten organizations, including Planned Parenthood affiliates, community clinics, and provider networks.*

The programs profiled here illustrate the range of perspectives and experiences of family planning providers and the evolution of these providers in the managed care environment. The information for these case studies comes from extensive telephone interviews with the executive directors and staff members of the family planning programs and is supplemented by other relevant documents provided by the organizations.

The scope of the project did not permit interviews with representatives from the health plans involved with these family planning agencies. Therefore, information on the motivations and incentives of the health plans reflects the perceptions of the family planning organizations. The interviews focused on organizational mission; relationships with managed care plans, including services covered in contracts, financial arrangements, and control issues such as prior approval; incentives for the organization and the health plan to enter into a relationship; confidentiality issues; noteworthy problems; and contextual factors that have influenced the process and outcomes.

Planned Parenthood of Northern New England—A Businesslike Approach in a Supportive Political Environment

Planned Parenthood of Northern New England (PPNNE) is a private, nonprofit health care organization with a comprehensive network of 27 gynecologic centers in Vermont, New Hampshire, and Maine serving more than 49,000 patients. Like most family planning organizations attempting to link up with managed care networks, PPNNE believes that these relationships will enhance its financial stream and help it to retain clients who prefer Planned Parenthood but cannot use their managed care plan benefits. In addition, PPNNE did not want to be relegated to providing only abortions and vasectomies.

The strategic plan of PPNNE is to prepare for possible changes associated with health care reform and the evolution of managed care in its regional area. Although 90% of patient visits fall under the category of comprehensive family planning services, PPNNE has been expanding the scope of its services into primary care and the full spectrum of women's health care. In metropoli-

*The organizations consulted for this article are Planned Parenthood of Minnesota; Planned Parenthood Health Services of Northeastern New York; Planned Parenthood of Northern New England; Planned Parenthood Association of Santa Clara and San Benito Counties, California; Planned Parenthood of Seattle; Planned Parenthood of Shasta-Diablo, California; Delta Health Center in Stockton, California; Women and Children's Health Center in Visalia, California; Tri-City Health Center in Fremont, California; and Family Health Council, Inc., in Pittsburgh, Pennsylvania.

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ABBREVIATIONS USED IN TEXT

CPT = Current Procedural Terminology
FHC = Family Health Council
HIV = human immunodeficiency virus
HMO = health maintenance organization
PPHSNNY = Planned Parenthood Health Services of Northeastern New York
PPM = Planned Parenthood of Minnesota
PPNNE = Planned Parenthood of Northern New England
STD = sexually transmitted disease
VMC = Vermont Managed Care

tan centers such as Burlington, Vermont, expansion into women's health care includes a full range of gynecologic services and surgical procedures through a physician's practice. One rural health center, reflecting the expansion into primary care, also offers prenatal services, well-child visits, and primary care for women and children.

Although it is working to establish relationships in New Hampshire and Maine, PPNNE's early negotiations have focused on Vermont. Contracts or letters of commitment have been signed with four managed care plans since January 1994, when a contract was signed with Vermont Managed Care (VMC), a plan for University of Vermont employees. The contract is based on discounted fee-for-service whereby subscribers can come directly to Planned Parenthood without referral from a primary care provider to obtain an array of gynecologic services, including testing for sexually transmitted diseases (STDs) and the human immunodeficiency virus (HIV). If a patient chooses to have PPNNE communicate with the primary care provider, PPNNE receives 90% reimbursement of the fee for the service (plus 5% withheld at year end, based on the plan's overall performance). If a patient wants the visit with PPNNE to remain confidential, PPNNE receives 80% reimbursement of the fee from VMC and the remainder is billed to the patient. Patients seeking abortion, vasectomy, and colposcopy services must be referred by the primary care provider to receive reimbursement.

In this instance, VMC was the initiator of the contract because many of its clients were extremely unhappy that they could not continue using Planned Parenthood and its gynecologist, who had originally practiced at the university health center. As a novice managed care player, VMC was willing to experiment with this new type of relationship because it saw the inclusion of PPNNE as a way to attract and keep its client base.

Because the client base is limited to University of Vermont employees, this contract pertains only to the Burlington clinic, which sees 20 to 25 patients per month. Most patients choose to share information about their visits to Planned Parenthood with their primary care providers, and payment is comparatively prompt.

Implementation of the partnership was somewhat difficult because of VMC's reluctance to view PPNNE as an organization rather than as the two physicians who worked for them. Originally, VMC listed only the physicians' names in its directory; after Planned Parenthood clarified its organizational structure, VMC listed the entire organization.

A participating provider contract for the Blue Cross/Blue Shield indemnity insurance plans was signed in November 1993, followed by a contract with the Blues' managed care product, Vermont Health Partnership. Under this contract, patients may come to PPNNE for one visit annually without referral from a primary care provider. Any services beyond that visit must be referred by the primary care provider to be eligible for reimbursement. Planned Parenthood will be reimbursed according to the Blues' "maximum allowable" fees for services provided.

Although becoming a participating provider with the Blues' indemnity plan was not a problem, the negotiation process took approximately a year. After collecting and analyzing a substantial amount of data and cost information from PPNNE, the Blues decided to follow the one-visit route rather than capitate services. The fact that PPNNE does not have 24-hour access for patients was also a stumbling block, as the Blues are accustomed to offering this service as part of their normal health care package.

Blue Cross/Blue Shield's motivation to develop a relationship with PPNNE was twofold. First, they wanted to gain a competitive advantage over Community Health Plan (CHP), the largest health maintenance organization (HMO) in the state. Additionally, political pressure was felt in 1994 during the health care reform debate in Vermont. Although legislation failed to pass in the spring, PPNNE was treated favorably throughout the legislative process. Public officials and managed care plans viewed PPNNE as an organization that should be included in the negotiations.

Implementation of the participating provider contract was complicated by PPNNE's internal limitations in relation to the institution of the entire third-party billing process. In the past, Planned Parenthood has not billed third parties. Building this capability internally was a staggering process.

The process that PPNNE is now undergoing to obtain credentials for its practitioners under the Blues' Vermont Health Partnership has been complicated, slowing the implementation process by another month. Additionally, administrative staff report that the managed care provider representative's lack of knowledge about what PPNNE does and the breadth of its services causes some confusion regarding the details of how contracts will actually work.

Planned Parenthood has a written commitment with CHP in Vermont (a staff-model HMO) to enter into a contract in early 1995. This contract will allow CHP subscribers to come to PPNNE without a primary care provider referral for one visit annually, similar to the arrangement in effect under the Blues' Vermont Health Partnership. Similar to the Blues' plan, Community

Health Plan was also motivated to form a partnership with PPNNE because of political and market pressures. As a traditional closed-panel HMO, however, CHP entered into discussions reluctantly.

With respect to the issue of confidentiality, PPNNE emphasizes to patients who wish to use insurance that confidentiality cannot be guaranteed because PPNNE cannot control what an insurance company does with medical records once they are outside its system. If PPNNE bills the patient's insurance, the patient must sign an authorization for the release of information and must understand that the insurance company will have access to the patient's medical records to process the claim. This is particularly important for patients seeking abortion services and HIV testing. In fact, PPNNE staff members usually discourage patients from billing for HIV testing because they think the insurance company may act on the information. PPNNE cannot accept the insurance of a patient who is reluctant to receive mail for any reason. Planned Parenthood's billing service company has signed a confidentiality agreement and will not release patient information to anyone outside the PPNNE organization without the patient's consent.

The experience of PPNNE demonstrates the importance of a businesslike approach by the family planning provider. A supportive political environment, accompanied by special attention from a new health plan whose subscribers preferred PPNNE, provided a context that made it possible for this organization to move ahead with its strategic plan of integration.

Planned Parenthood Health Services of Northeastern New York—Expanding Into Primary Care

Administrative staff members at Planned Parenthood Health Services of Northeastern New York (PPHSNNY) report that they have been in the process of turning their organization upside down. PPHSNNY signed its first contract with an HMO in 1993, moving toward the introduction of primary care services at its clinics in upstate New York.

The organization serves 14,000 persons annually at nine locations: seven rural sites, one urban center, and a suburban clinic. It began offering comprehensive primary care at the Schenectady clinic in December 1993 and is in the process of expanding primary care services to its other locations. Prenatal services up to delivery are available at three sites, and arrangements have been made with three hospitals to handle deliveries.

The executive director of PPHSNNY views the contracts with managed care organizations and expansion to primary care services as the convergence of several paths. Through discussions in focus groups, Planned Parenthood determined that its patients wanted and needed primary care. Consultants advised the organization that pursuing the possibility of third-party reimbursement could add substantially to its revenues over time, perhaps by as much as $350,000 annually after five years.

Staff members of PPHSNNY think that expanding into primary care and development of relationships with third-party payors is the best way to secure the future of its family planning mission. To make full use of third-party reimbursement, the organization has computerized eight of its nine sites and added staff who track insurance claims and manage Medicaid reimbursement. Because a large percentage of the population in upstate New York is enrolled in HMOs and the state has the goal of moving large blocks of Medicaid patients into managed care, PPHSNNY initiated talks with the managed care health plans.

Staff members state that an entire year was wasted trying to interest HMOs in developing a relationship. These attempts were rejected by the head of each managed care organization during the initial round of visits. The plans could not classify Planned Parenthood as specialists or primary care providers. The plans only understood the concept of signing up physicians and could not envision listing an agency in their subscriber manuals.

Based on these experiences, PPHSNNY adopted a different strategy. It approached the six physicians who worked for it part-time and asked if PPHSNNY could act as their agents in negotiations with the HMOs. With this approach, the plans were willing to talk because of their interest in the client base that used Planned Parenthood, particularly in rural areas. The names of the physicians, their office addresses, and PPHSNNY's address were then listed in the subscriber manuals.

The first three managed care contracts were the most difficult to negotiate. All are fee-for-service arrangements and include family planning, gynecologic, and obstetric care. Counseling services are generally not covered. Some arrangements also reimburse PPHSNNY for its gatekeeping role. Collaboration with one HMO that had multiple point-of-service offerings was like developing relationships with 15 HMOs, each with its own issues to be negotiated. Planned Parenthood Health Services of Northeastern New York has signed its first capitation contract with a staff-model HMO to provide abortions for $500 per patient. Under this contract, a patient can waive the referral process; instead, a summary of the services performed is sent to the primary care physician.

Confidentiality issues are still being clarified and continue to be a concern. Planned Parenthood Health Services of Northeastern New York has had to change its policies dealing with patients because of the number of people who have access to charts. Initially, PPHSNNY staff members would tell patients whether or not their carrier would send an Explanation of Benefits (EOB) to the home of the subscriber. Because of the increasing number of carriers with which they have relationships, it has become difficult for staff to remember which ones do or do not send EOBs. The new approach is to tell patients that an EOB is likely to be sent to their home. If patients have used the insurance in the past, they know whether an EOB will be sent to the subscriber. If they

have not used their insurance before, this notification puts responsibility on the patient to consult the carrier and find out whether they send EOBs. Planned Parenthood staff encourage patients to call their carrier with questions.

Planned Parenthood Health Services of Northeastern New York's strategy of moving toward primary care as a means of preserving its original mission and serving patient needs is becoming more common among some family planning providers. This is particularly true in areas where health plans are concerned about the shortage of primary care professionals and view collaboration with providers of family planning as a positive strategy for attracting subscribers in rural communities.

Planned Parenthood of Minnesota—Maintaining a Focus on Reproductive Health

Unlike the two previous cases, Planned Parenthood of Minnesota (PPM) sees its future role as that of a special-niche player providing family planning services and related reproductive health care. The organization has no interest in becoming a comprehensive primary care provider. Its services are available through 25 clinics in Minnesota and one clinic in Sioux Falls, South Dakota. Nearly 60% of PPM's patients come from outside the Twin Cities area (Minneapolis/St. Paul). For many patients who live in rural areas and small communities, Planned Parenthood is often the only source of medical care. Planned Parenthood of Minnesota's strategic plan is understandable, given the health care marketplace and political environment in Minnesota.

Health maintenance organizations are widespread in Minnesota, particularly in the metropolitan areas. The dominance of managed care resulted in recent state legislation designed to provide greater provider access. Since 1992, Minnesota has been making plans for statewide expansion of managed care. In anticipation of the effect of managed care on their clients and missions, the state's family planning providers, led by Planned Parenthood, successfully advocated for legislation in 1993 that established freedom-of-choice requirements for Medicaid managed care patients seeking family planning services. This legislation was expanded in 1994 in two important ways. First, the freedom-of-choice provisions now cover voluntary family planning, diagnosis of infertility, testing and treatment of STDs, and testing for HIV and HIV-related conditions. Second, under an "essential community provider" provision, health plans in the state must enter into provider participation agreements with health providers that are deemed essential because they serve low-income and underserved populations, are public or not-for-profit, and do not restrict access for financial reasons. Planned Parenthood of Minnesota staff believe that its clinics will be designated essential community providers in 1995.

In the past, PPM has had a limited relationship with some of the health plans to provide abortions on a fee-for-service basis. In May 1994, the Henry J. Kaiser Family Foundation sponsored a meeting with the heads of all of the health plans and PPM. Before that session, the possible relationship between managed care and reproductive health providers in Minnesota had not been discussed. What became apparent during the meeting was that the development of relationships was not a high priority for the plans, although philosophically they were supportive of PPM's presence.

Since that meeting and the final passage of the legislation, PPM has signed contracts with two managed care plans and is involved in negotiations with three others to formalize and clarify what is required by the legislation. In each of these cases, the negotiations or contracts include family planning, treating STDs, and abortions. All of the contracts are fee-for-service arrangements, which is preferred by PPM because of the unpredictability and financial risk associated with capitation.

Planned Parenthood of Minnesota staff report that, although there is no philosophical disagreement with the plans, the managed care organizations do not know how to implement the legislation and work out the operational details of the relationship. For instance, the major staff-model HMO says it wants to comply with the new laws that go into effect in 1995, but it does not have a good idea about how to handle the payment issues and wants PPM to explain how to comply. Its recently negotiated plan for all abortion services is expected to become the basis of the contract that includes family planning services.

From a pragmatic point of view, PPM staff report that the Kaiser meeting with the heads of the plans has been crucial in moving toward implementation of these relationships. Having a face-to-face relationship with high-level management has resulted in a better response from and more successful interactions with the middle-level staff of the plans.

Planned Parenthood of Minnesota also cites confidentiality as an important issue, but is most concerned about its Medicaid patients. For services provided by PPM, all billing codes will be suppressed by the state. Confidentiality arrangements are reviewed carefully on a contract-by-contract basis so as not to compromise patients' privacy.

California—The Response of a Community Clinic and a Planned Parenthood Affiliate

The recent mandate in 13 counties to move all Medi-Cal clients into managed care provides a different context for many family planning providers and community clinics in California. Medi-Cal patients in these counties will choose between two plans—the local initiative designed to serve as a safety net and a commercial plan. The following cases illustrate briefly how some family planning providers are responding to yet another environment.

Planned Parenthood—Shasta-Diablo

This Planned Parenthood affiliate defines its mission in terms of its clients, not the services it provides. Its goal is to serve primarily poor women and children with an emphasis on preventive primary care and reproductive health.

In California, Planned Parenthood is making a county-by-county and clinic-by-clinic decision about relationships with managed care organizations. With 50% to 60% of its patients on Medi-Cal, it must be a participant in those counties affected by the state initiative. In this context, the organization has contracted with the county-organized health system in Solano County. The new plan courted Planned Parenthood because it operates three sites where poor people reside, and it has a concern about a shortage of primary care facilities and staff. The plan and all providers went on line in May 1994. As a result of this contract, Planned Parenthood will eventually gain about 2,500 new clients. Trying to keep up with billing and whole new categories of CPT [current procedural terminology] codes is challenging, but the organization has purchased a new computer system and increased staff costs through foundation grants.

Six months into the relationship in Solano County, the future for it is uncertain. Receiving a capitation rate of only $8.16 per member per month, Planned Parenthood estimates that it may lose as much as $200,000 a year. The staff is concerned about the agency's ability to provide high-quality care for Medi-Cal clients at this rate. Planned Parenthood is assessing whether to continue the partnership or terminate it. If Planned Parenthood moves away from the relationship and loses its enhanced capacity, however, staff members are worried about their ability to serve other low-income clients who do not qualify for Medi-Cal.

Confidentiality has not presented a problem from Planned Parenthood's point of view. The staff does not send a record to the primary care provider without the patient's consent.

Tri-City Health Center—Fremont

Tri-City Health Center is a community-based, nonprofit health organization that provides primary health care, gynecologic services, pediatric services, prenatal counseling, and education to those who are economically disadvantaged and face substantial barriers to health care in parts of Alameda and Santa Clara counties. Tri-City Health Center is part of a network of community clinics that are now in the process of incorporating so that they will be better positioned in the new environment to negotiate with the managed care health plans and county HMO. By working as an incorporated network of providers, the community clinics in the area hope to enhance their leverage with the health plans, coordinate their marketing for clients, and share expensive resources such as computer technology and staff.

Although Tri-City Health Center has an excellent understanding of the needs of the Medi-Cal population, staff members are concerned about the lack of capital funds and technical experience needed to reorganize the agency in a more businesslike fashion to meet the financial and informational needs of managed care plans. Forming a network is seen as an important step to take advantage of the strengths of each clinic without duplicating one another's efforts. Thus far, four clinics have been admitted to the incorporated network.

Pennsylvania—Collaboration With Family Planning Networks

Like the small group of community clinics in California that are trying to form a network to collaborate with managed care plans, provider organizations in Pennsylvania have already found this to be an effective strategy for negotiating favorable contracts with health plans. Representing 21 health care agencies that provide family planning and reproductive health services in a five-county area, the Family Planning Council of Southeastern Pennsylvania coordinated a single response to mandated Medicaid managed care for Philadelphia's community of family planning providers in 1986. The freedom-of-choice requirement, the large number and variety of providers that would be covered by a single contract, and the reputation of the council's professionals to provide high-quality, cost-effective care proved to be important factors in an HMO's decision to enter into an agreement with the council. Experience with the initial HMO established a favorable context for similar contracts with other managed care plans that have entered the marketplace.

Offering reproductive health care at more than 50 sites in western Pennsylvania, the Pittsburgh Family Health Council (FHC) has recently established relationships with two HMOs. After observing the successful experience of the Family Planning Council of Southeastern Pennsylvania and the increased inroads made by managed care, Pittsburgh FHC voluntarily initiated discussions with the two health plans. Although the relationship was not a high priority for either plan (discussions lasted almost two years), in the end the managed care organizations were interested in gaining access to 50 clinics in urban and rural communities with just one set of negotiations. The federal freedom-of-choice requirement for Medicaid clients and low pricing for contraceptive supplies also provided incentives for the plans to contract with Pittsburgh FHC.

As umbrella organizations, the Family Planning Council and Pittsburgh FHC have successfully developed relationships with managed care organizations on behalf of their affiliates because they provide coordinated financial and management services, removing much of the burden associated with complicated billing systems and dealing with multiple health plans. Their businesslike approach and experience handling centralized billing enhance their negotiating position with managed care organizations on behalf of their members.

Conclusion

The examples of developing relationships between family planning agencies and managed care organizations provided here illustrate several common themes. First, each partnership is unique based on important contextual factors such as the penetration of managed care in the local market, the patient profile of the clinics, state laws, and the providers' previous relationships with insurance companies and health plans.

Second, taking the time to develop relationships with family planning providers is not usually a priority for health plans unless they are confronted with mandates, a shortage of patients, or a shortage of primary care providers. To the extent that managed care plans are interested in collaboration, they prefer dealing with networks of providers where one set of negotiations results in relationships with many clinics and patients. Depending on the state or region, Planned Parenthood may have an advantage in terms of name recognition and organizational clout. The experience of the provider networks in Pennsylvania suggests that the Planned Parenthood name is not necessarily the key factor, however.

Third, family planning providers are increasingly moving toward expansion of their services into primary care. Community clinics and Planned Parenthood affiliates are responding to patient needs and their sense that a more comprehensive mix of services makes them more attractive partners to managed care plans.

Finally, most of the contracts between plans and family planning providers are fee-for-service rather than capitated arrangements, reflecting the view of health plans that family planning providers are offering a specialty service.

Because the relationships between family planning agencies and managed care health plans are still developing, any evaluation of those relationships' effect on the organizations and their patients would be premature. Two issues clearly require more monitoring and discussion as these types of collaborative efforts move forward—confidentiality and technical assistance for family planning providers.

Generally speaking, confidentiality has not proved to be a barrier to the initial collaboration and contract negotiations between the family planning agencies and plans because details related to confidentiality are often left to be negotiated after contracts are signed. If patients have concerns about a paper trail coming to their homes or the primary subscribers, family planning providers often advise them to pay out of pocket rather than use their insurance benefits. The other option offered to patients is to sign a form that releases their records to the health plan. Given that confidentiality and lower cost are two primary reasons family planning clinics are attractive to patients, this is a problematic approach. Additional attention should be devoted to detailing the specifics of confidentiality during the initial contract discussions, using strategies adopted by other organizations such as the Family Planning Council of Southeastern Pennsylvania, which has negotiated arrangements with health plans under which it provides an unlinked report that documents services provided and the number of patients seen but does not reveal identities.

Another area of concern relates to the ability of family planning providers to organize themselves in a businesslike fashion in preparation for the negotiation and implementation of these new relationships. Because these agencies have been mission-driven rather than market-driven, they are not usually set up to handle third-party reimbursement, deal with the Medicaid system, or review detailed contracts. This may put family planning providers at a disadvantage in developing relationships with managed care plans. Networks like the family planning councils in western Pennsylvania and Philadelphia have been better positioned to negotiate with the health plans because of their technical expertise. More attention needs to be devoted to understanding the kind of technical assistance and financial support needed by family planning agencies as they move through this time of transition.

THE HENRY J. KAISER FAMILY FOUNDATION

Family Planning, Managed Care, and Rural America

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Within the United States, rural residents encounter a greater number of barriers in accessing health care services than their urban counterparts. In general, rural Americans have less access to both family planning services and managed care delivery systems. Given the rapid changes in health care, we reviewed the implications for the provision and integration of family planning and managed care services in rural areas, where there is limited experience in establishing working relationships between those services. In many instances, family planning services are well established in rural areas where managed care has not yet penetrated. Our case study in Minnesota suggests that, although managed care and family planning services are developing in rural areas, there is little evidence of collaboration. Several innovative and successful family planning projects do exist in rural areas, however, and serve as models of successful population-based programs that could work well with health plans. Although this study concentrated on the provision and utilization of subsidized family planning services, there is a compelling need for further work to determine accurately where rural residents are accessing such services and how the expansion of managed care will affect the delivery of reproductive health care.

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As managed care companies and family planning providers prepare themselves for the inevitable changes in the health care delivery system, many of these organizations are attempting to define future relationships. Whereas much of the discussion focuses on urban issues, nearly a quarter of Americans live in nonmetropolitan or rural areas, and this fact presents health care policymakers with serious challenges.[1]

Previous studies that have addressed the health beliefs of urban and rural populations have found differences in the definition of health and the perception of health status between these two groups.[2,3] This presents difficulty in making direct comparisons between rural and urban residents. Furthermore, such comparisons are lacking with respect to reproductive health.

The unique family planning needs and concerns of the rural population warrant attention as managed care expands from urban centers. Family planning clinics have traditionally played an important role in the health care of women in rural areas, often serving as the only available means of ensuring privacy in the access of family planning services. In addition, these clinics are often the closest health care location. Thus, their experience and expertise in the delivery of reproductive health care to rural women cannot be overlooked. The following discussion focuses on the current delivery of family planning services and the expansion of managed care in rural America, including a case study of rural Minnesota and the potential relationship between family planning organizations and managed care systems.

Family Planning Services in Rural Areas

An accurate assessment of availability and access issues regarding family planning services in rural communities is limited by the lack of comprehensive national data and the failure of existing data to differentiate between urban and rural sites. Planned Parenthood, for example, is a major provider of family planning services in rural areas through its 170 affiliates. Each affiliate has an average of 5.5 satellite clinic sites, some of which may be located in nonmetropolitan areas. For reporting purposes, however, the affiliate reports the total number of women seen by all its clinics, not distinguishing between urban and rural clients.

Although previous studies have attempted to address the problem of "unmet need" and family planning programs, much of the research has been performed in developing countries, and results have been inconsistent due to the different criteria employed to define unmet need.[4] The specific issue of unmet need in rural family planning has not been adequately addressed.

In addition to Planned Parenthood clinics, public family planning services are provided in rural areas throughout the country by hospitals; city, county, regional, and state health departments; community action groups; neighborhood health centers; community and migrant health centers; Native American nations;

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family planning councils; and other organizations.[5] State and local health department clinics are well represented in rural areas, whereas fewer than half of the Planned Parenthood affiliates that cover rural areas actually have rural clinics.

The distribution of these providers varies from state to state. In Texas, for instance, Planned Parenthood (along with other types of clinics) provides services in rural and urban counties throughout the state. North Dakota, on the other hand, has no Planned Parenthood affiliates, and family planning services are provided primarily through a federally funded, state-run program.

Planned Parenthood is not the only provider of family planning services in rural areas, but it is one of the few to study the situation on a national level. Recognizing the family planning needs of rural populations and the lack of information on the subject, a national survey of Planned Parenthood affiliates was conducted in 1990 by the Western Region Assembly of Planned Parenthood.[6] Although results of the survey pertain to Planned Parenthood clinics, other organizations identify similar circumstances in areas they serve. Poor transportation, poor access to health care, and poverty were indicated in the survey as predominant characteristics of rural areas. Because access to medical care is inadequate in many rural areas, existing family planning clinics often serve a broader community need.

In the survey, Planned Parenthood clinics identified barriers they face in meeting rural needs, including the lack of funding, the difficulty of reaching remote areas, and the absence of medical personnel. Many affiliates mentioned the need for special marketing efforts and service delivery strategies in rural areas, namely using the county hospital as a clinic site and offering free clinics and free pregnancy testing. In addition, the survey found that thriving rural programs had good relationships with other community agencies, maintained extensive outreach and community involvement, possessed strong education programs, and ensured confidentiality.

Planned Parenthood directors in Texas and Washington who were interviewed for our study emphasized the importance of privacy and confidentiality for their rural clients. Anonymity in seeking family planning services is often cited as a serious concern for rural women, particularly teenagers who do not want their parents to know they are sexually active. Buying condoms at the local drugstore or requesting birth control from a family doctor can be problematic for that reason. Family planning clinics help preserve anonymity in small rural communities. The director of a family planning program in North Dakota noted that despite the generally conservative views of the rural population, family planning clinics are perceived as valuable by the communities they serve.

Managed Care in Rural Areas

Managed care concepts, such as health cooperatives, organized medical care programs, and prepaid group practices were first introduced in rural areas almost 150 years ago as a solution to problems of health care access and availability.[7] In recent years, however, most of the expansion of managed care has occurred in heavily populated states with large urban centers. Although comprehensive information pertaining to the expansion and success of managed care in rural areas is limited, these data indicate that some states with large rural populations have experienced an increase in rural penetration of health maintenance organizations (HMOs) in the past several years. The limited number of rural managed care plans suggests that some urban-based HMOs are expanding into rural areas and improving access for residents. Clinic networks in Tupelo, Mississippi, and Rugby, North Dakota, are examples of rural HMOs that are reportedly increasing the supply of primary care physicians and containing costs.[8]

The growth of managed care in rural areas has been limited by several factors. First, traditional managed care strategies are less effective in rural areas. In its early years, managed care focused on two strategies: negotiated discounts in physician fees in return for an increase in patient volumes; and a decrease in the duration of hospital stays. These cost-containment approaches have less yield in rural areas because physicians have already captured the available market of patients and reducing hospital stays may be less feasible unless outreach and home health services are well developed. The spread of managed care to rural areas is slower and less consistent for these reasons.

Second, rural residents are more likely to be uninsured. Fewer rural residents receive insurance from an employer. Thus, rural areas are less attractive to health plans.[9] The absence of widespread rural health plans to date means there is little experience in defining rural managed care and family planning relationships.

Some Planned Parenthood affiliates in rural areas have begun contracting with managed care companies. Planned Parenthood of Seattle is expanding its scope of services at rural sites to include additional primary care services to appeal to the managed care market. In many of the areas served by this affiliate, residents live in remote locations where access to health care is limited. Women are likely to use the family planning clinic as their primary source of care. The move to include additional primary care services is viewed as a necessary change to meet local needs.

Rural Minnesota: A Case Study

To examine closely the relationship between family planning and managed care, we selected rural Minnesota as a case study. Minnesota is a state with a well-developed family planning system, including a strong Planned Parenthood presence in rural Minnesota and well-established managed care organizations.

Although health care services in Minnesota are advanced compared to the rest of the country, stark differences become evident when comparing rural and

urban areas. Hospital and physician services are largely concentrated in urban areas where 87% of physicians practice. Of those practicing in rural areas, 68% are considered primary care physicians. Approximately one primary care physician practices for every 78 square miles.[10] Substantial portions of rural Minnesota are designated as medically underserved according to federal regulations.

A third of Minnesota's 4.5 million residents live in rural areas. Although most rural Minnesotans are of European descent, a significant number are Native American or Hispanic. Poverty is more prevalent in rural Minnesota than in the Minneapolis-St. Paul metropolitan area.

When compared with their urban counterparts, rural residents are less likely to have health care insurance. If they are insured, they are more likely to have purchased individual rather than group insurance and have fewer covered benefits and higher out-of-pocket health-related expenses.[11]

With regard to managed care, significant differences are apparent between rural and urban regions. In 1992, in the Twin Cities area, 44% of residents were enrolled in an HMO, whereas only 11% of residents of predominantly rural northeastern Minnesota belonged to an HMO. In the rest of rural Minnesota, there is very limited health plan enrollment. Presently, Medicaid beneficiaries are enrolled in health plans in only one county, but this program is slated for expansion in 1995. As many rural counties have a relatively large percentage of Medicaid recipients, this initiative will significantly affect statewide HMO enrollment.

Family planning in Minnesota, as in many states, is supported by both federal and state funding. In 1994, $12.7 million was designated for family planning use in Minnesota. The Family Planning Special Projects grant, Minnesota's principal source of state funding, allocated $1.1 million in 1989. At that time 32 counties in the state had no subsidized family planning services. Since then, funding has increased markedly. The Minnesota State Legislature has recently increased state support of subsidized family planning. In the 1994-1995 biennium, $3.8 million is available for family planning programs, including private physicians who offer family planning services to low-income patients in remote areas. Allocation of funding is determined according to a needs-based formula, and 52% of this budget has been granted to organizations within the Minneapolis-St. Paul metropolitan area. Due in part to the increase in funding, the number of counties in Minnesota that receive no subsidized services has been reduced to 13. This initiative has had a significant effect on expanding services in rural areas.

Rural family planning is provided primarily by Planned Parenthood of Minnesota and its delegate agencies. Together they provide 37 clinics, serving a total of 32 counties. In 1993, 33,184 clients attended these rural clinics. An age breakdown indicates that 38% of those attending were aged 19 years or younger, 54% were between the ages of 20 and 29, and 8% were older than age 30.

Rural and urban Minnesota youth differ somewhat in frequency of sexual activity. No difference has been found in the frequency of intercourse at the junior-high-school level. Urban youth, however, report more frequent intercourse than rural youth at the senior-high-school level.[12]

A greater contrast is noted in the contraceptive profile of urban and rural Minnesota youth. Sexually active urban youths are more likely to use contraception in general and have a higher rate of use of prescription methods of birth control. Rural youths who do use birth control tend to use condoms or over-the-counter contraceptives and tend to use them with less consistency.[13]

Rural Minnesotans face access barriers to family planning services typical of other rural areas. As in other parts of the country, some rural Minnesota communities have strong conservative opposition to family planning. This opposition has resulted in protests at clinics, and in 1994 there was an arson attack on a long-standing Planned Parenthood clinic in Brainerd. To address this barrier to access, Planned Parenthood of Minnesota provides support for the expansion of rural clinics. A Community Educators Network has also been established to provide workshops for family planning practitioners. The goal of the program is to help providers resolve conflicts with opponents to family planning services.

Family Planning Programs in Rural Minnesota

Because no comprehensive information exists on managed care and family planning in rural Minnesota, we looked at three areas of the state: Freeborn County in southern Minnesota, the Rum River area in central Minnesota, and Outlook Health Services in east-central Minnesota. In each case, we found well-developed rural family planning services with little link to managed care.

Freeborn County. Freeborn County is a rural county on the Minnesota-Iowa border. Family planning services are available through Planned Parenthood at one private medical clinic and two satellite clinics. The satellite offices are staffed by three gynecologists, one of whom is female, and three nurse practitioners. These clinics are primarily supported by federal funds.

The clinics offer clients, most of whom are under the age of 24, access to a comprehensive range of family planning methods, education, and counseling. The main clinic is centrally located and a little more than one block from the high school attended by most high school students in the region. In spite of the existence of the centrally located, easily accessible, and comprehensive family planning clinic, teenage pregnancy rates in the county remain higher than the state average.

Planned Parenthood of Minnesota has provider status with several state managed care plans, but membership in those plans is low in Freeborn County. Under the Medicaid initiative, these clinics will interact more with

managed care. To date, there is very little contact between the two groups.

Rum River Women's Health Project. The Rum River Women's Health Project is a nonprofit agency providing family planning services at seven sites in the counties of Mille Lacs and Sherburne, just north of the Twin Cities metropolitan area. The project was founded in 1986 in response to a report that emphasized the high rate of teenage pregnancy in the region and the lack of family planning services.

Although Mille Lacs and Sherburne are neighboring counties, some economic differences are evident. Data compiled in 1990 indicated that in Sherburne County, 22% of the population had incomes below 200% of the poverty level. Less than 9% of the population was eligible for Medicaid. By comparison, 40% of the population in Mille Lacs County had incomes below 200% of the poverty level, and almost 20% of the population was eligible for Medicaid.

In 1993 the Rum River project served 250 clients, an attendance rate that represented only about 10% of those considered at high risk of unintended pregnancy as determined by age or poverty status. One explanation for such low utilization of services could be remaining access problems. For example, the main clinic in the town of Princeton is located about one mile from the local high school. Considering the severity of Minnesota winters and the lack of public transportation, even this relatively short distance may render services inaccessible to local teenagers. Like the Freeborn County sites, this agency has little interaction with managed care organizations at present.

When considering 1992 data for those between the ages of 15 and 19, Mille Lacs County had the 14th highest birth rate in Minnesota, whereas Sherburne County ranked 49th among the state's 87 counties. Despite higher birth rates, practitioners are aware that fewer adolescents in Mille Lacs County are choosing to have abortions. This is confirmed by data available for 1990 and 1991 that demonstrate a reduction in induced abortions from 34% of all pregnancies among 15- to 19-year-olds in Mille Lacs County to 24% in a one-year period. Although the actual reduction in the number of induced abortions in this group was small (from 23 in 1990 to 10 in 1991), local practitioners are encouraged by the trend. These statistics may suggest that a significant number of adolescent pregnancies are planned, a hypothesis strongly supported by experience of rural family planning practitioners. The same magnitude of reduction in abortions is not evident in Sherburne County.

Outlook Health Services. Adjacent to Mille Lacs and Sherburne counties are Kanabec, Isanti, and Chisago counties. A nonprofit agency known as Outlook Health Services, Inc., was established in October 1991 to provide family planning services for this three-county region. A comprehensive range of services is provided, including counseling, method services, referral, and follow-up.

In 1993 Outlook Clinic served 792 clients. A steady increase in client caseload has occurred at each site. As is the case with other subsidized clinics, clients are assessed fees according to their income and ability to pay. More than 96% of the clients attending Outlook Clinic fall into the high-risk category of less than 200% of the poverty level. In 1993, statistics show that 36.9% of those attending were either younger than 19 years or older than 35, and more than 30% had less than 12 years of education.

The major goal of the project is to decrease the proportion of unplanned pregnancies in the geographic area, particularly among women considered at high risk for unintended pregnancies.

The teen birth rate in the counties served has declined markedly since inception. Data compiled by the Children's Defense Fund for 1980-1984 listed Kanabec County as having the second-highest teen birth rate in the state. Isanti County was ranked 17th, and Chisago County was ranked 20th.[14] This contrasts with 1992 data on teen birth rates that ranked Kanabec, Isanti, and Chisago counties in 28th, 31st, and 38th place, respectively.

The services provided by Outlook Clinic are supported almost entirely by public boards with little, if any, managed care contact at present.

Managed Care in Rural Minnesota

Although managed care is well established in Minnesota, it is not yet well established in the rural areas of the state. To date, few rural Minnesotans are enrolled in health plans.

Supported by state health care reform legislation, the state's large managed care organizations have committed to a strategic plan to build better relationships with public health organizations, including family planning; however, these efforts are in their beginning stages. Consequently, rural family planning clinics at present see very few managed care members.

The innovative family planning projects discussed above have several features in common, including staff formally dedicated to family planning. Furthermore, successful programs are population based, closely linked to the community, and supported by local doctors, nurses, and teachers with access as the primary objective. These features have been previously identified as vital components of successful programs and are likely to indicate key characteristics of successful managed care and family planning services.[15]

As managed care in Minnesota continues to expand and involve more rural communities, the existing rural family planning clinics could well serve as models of successful, population-based programs. Managed care programs committed to building on local public health initiatives can strengthen these existing efforts by expanding the patient base and reducing dependence on unstable federal funding. One benefit of that scenario could be further expansion of family planning to rural sites currently without adequate access. Such an

approach would require any competing health plans operating in a rural region to cooperate in providing family planning services. Cooperation between plans is likely to best ensure a critical mass of dedicated staff, a practitioner base and the support of the community.

Conclusion

The provision of family planning services and the presence of managed care in rural areas vary widely throughout the country. In some regions, managed care is nonexistent and family planning clinics are the only providers of care. In other areas, managed care exists but has no relationship with local family planning providers, whereas in some communities, managed care organizations and family planning providers are collaborating to meet the needs of rural residents. Because of this diversity, it is difficult to predict how rural managed care and family planning will interact in the future.

This lack of experience, and the lack of useful data or research on rural family planning, limit our observations. We suspect, however, that rural areas will confront similar issues to those addressed in urban areas regarding the collaboration of managed care and family planning. The problems of low population density and a shortage of health care practitioners combine to make access to family planning difficult. These same issues combine to slow the growth of managed care in these regions. Finally, the issues of privacy and confidentiality are more acute in rural areas because community mores are frequently more conservative and there are few, if any, venues for anonymous purchase of contraceptives.

The continuing development of managed care and family planning services in rural areas offers exciting opportunities for the provision of family planning services that are part of a more integrated delivery system. The systematic enrollment of Medicaid beneficiaries in health plans will force family planning agencies and managed care companies to explore ways to work together and determine ways to serve their clients best. The need for further collaborative efforts between managed care and family planning providers is clear if duplication of services is to be avoided and integrated services are to be realized in the nation's rural areas.

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Promising Approaches for Adolescent Reproductive Health Service Delivery

The Role of School-Based Health Centers in a Managed Care Environment

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States throughout the United States are assuming an increasingly important leadership role in instituting health care reforms, primarily through the implementation of managed care financing and service delivery strategies. In so doing, they confront a central issue: how to ensure adequate access to health care services while simultaneously keeping expenditures under control. Concurrent with this rapidly increasing reliance on managed care has been the emergence of a school-based health center movement that, although still a fledgling effort in many respects, has in recent years begun to develop more extensively throughout the country.

Much of the impetus for the school-based health center movement has been the growing recognition that substantial numbers of children and adolescents lack adequate access to health care and that the type of care they need often goes beyond the parameters of traditional medical care. This is particularly evident for our adolescent population, for which, because of a variety of systemic, social, economic, and environmental factors and barriers to care, morbidity and mortality rates have increased substantially during the past decade.

As managed care programs continue to expand throughout the country, communities in many locations will face the challenge of developing a truly comprehensive and coordinated approach to care, particularly those communities that are implementing Medicaid managed care options where school-based health centers (SBHCs) are either in the planning stages or already in operation. For other communities where no such plans or operations exist, the lessons that have been learned by such centers may hold great promise for the development of more effective service delivery strategies, whether or not services are in fact provided on site in school settings.

In any assessment of managed care and SBHC systems, and whether they can be linked in some way to provide accessible, coordinated care for adolescents, a potential underlying philosophical conflict must be acknowledged: the conflicting priorities of SBHCs, which seek to increase access to care, and those of managed care programs, which must find ways to contain costs in an increasingly competitive medical services marketplace. Although the expansion of Medicaid managed care will increase access to a primary care physician for many low-income persons, states also expect providers to control overall use of services by relying on a system of fiscal gatekeepers. In contrast to managed care providers, because the focus of SBHCs has been on an age group that traditionally underuses services, the goal for most of these centers has been to increase appropriate service utilization, with a lesser focus on cost considerations.

Although both SBHC and managed care systems rely on a primary care approach to resolve the issue of access, managed care and SBHC providers appear at first glance to have little in common. Managed care providers have been uninformed about the existence of SBHCs in their communities or have perceived SBHCs as duplicating their own infrastructures, whereas SBHC proponents perceive managed care providers as inadequately responsive to the unique needs of the adolescent populations they serve.

These two systems have coexisted, with SBHCs often providing care to students who were already beneficiaries of managed care coverage.[1] With the rapid expansion of the Medicaid managed care system, which mandates that beneficiaries receive all care within a particular health maintenance organization (HMO) or managed care organization, HMOs are being confronted with a greater level of fiscal and community accountability for services provided to their beneficiaries. As SBHCs face restrictions on their ability to bill the Medicaid program for services they provide to a population that will also be enrolled in a managed care program, as well as other decreases in revenue sources, long-term financial sustainability will become even more difficult for them.

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ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
HMO = health maintenance organization
SBHC = school-based health center
STD = sexually transmitted disease

The purpose of this article is to describe the special health problems and service delivery needs of adolescents, the role of school-based service delivery models in responding to these needs, what is known about adolescents' use of managed care systems and SBHCs, and potential models for coordinating efforts between SBHCs and managed care programs. Although the focus of this article is primarily on Medicaid clients enrolled in managed care programs, many of the issues discussed here are applicable as well to people enrolled in traditional, commercial managed care plans, where employers (as opposed to the government) play a substantial role in subsidizing medical care.

Adolescent Risk-Taking Behaviors and Consequences

Adolescence is generally considered a healthy time of life, with most young people being spared the burden of long-term illnesses seen in older adults. In many respects, this is an ideal population for managed care health plans to target for enrollment and retention. However, the risk-taking behaviors of adolescents often result in negative outcomes that affect not only the adolescent, but the society as a whole.

Conventional concepts of medical care rooted in the biologic determinants of disease do little to address the serious health problems of adolescents because many of these problems are related to patterns of behavior adopted in response to their social, economic, and cultural environments. Despite these variables, however, most adolescent morbidity and mortality is preventable.[2]

Problems such as teen pregnancy, sexually transmitted diseases (STDs) (including infection with the human immunodeficiency virus [HIV]), suicide attempts, and injuries from violence or motor vehicle accidents (particularly while driving under the influence of alcohol or drugs) may lead to substantial, but preventable, costs.[3] For example, one in four sexually active adolescents will have a sexually transmitted disease before graduating from high school. Annually, approximately 3.8 million reported cases of STDs occur among adolescents ages 15 to 19 years old, including syphilis, gonorrhea, chlamydia, pelvic inflammatory disease, genital herpes simplex virus, and human papillomavirus infection. Based on estimated costs of $80 per case for office visits and laboratory tests, the national cost for treatment of STDs in adolescents in 1992 was estimated to exceed $880 million.[4]

In addition to the problem of STD prevalence, one out of ten adolescent females will give birth by the time she reaches the age of 18. Hospital and physician costs for live births to mothers 15 to 19 years of age represent another major health care expenditure. In 1992, the total annual cost of obstetric services for adolescents was estimated to be more than $4 billion nationally. In addition, in 1992, approximately 9% of adolescents who gave birth delivered a low-birth-weight infant, resulting in an additional annual cost of $1.5 billion.[4]

The cost savings of appropriately used and accessible preventive services in the areas of adolescent pregnancy and STDs alone could substantially decrease some of the enormous costs associated with these two social and public health problems.

Unless a variety of accessible services and health promotion strategies are included in health care and managed care reform efforts, however, adolescent health care costs are not likely to decline.

Delivery Needs for Adolescent Health Care Services

Adolescents have the lowest rate of primary care use of any age group in the United States.[5] Adolescents and young adults, especially those living in poverty, are also more likely to be uninsured than any other age group. Many other adolescents are underinsured, with coverage that does not include preventive care, counseling, substance abuse treatment, or other needed health care services. Adolescents also face behavioral and organizational barriers to care.

Many insured adolescents are unwilling or unable to make use of their coverage because they fear loss of confidentiality, they do not know what services are covered or how to file claims, or they cannot meet out-of-pocket co-payment requirements. Transportation and lack of access to or availability of services are particularly serious problems in rural areas. Health delivery systems, no matter how well organized or well meaning, cannot truly meet adolescent health care needs unless they can ensure adequate access to care and availability of all needed services. Other system factors are important as well, such as affordability, confidentiality, visibility, convenience, flexibility, and the willingness and ability to coordinate services as needed.

A scarcity of appropriately trained health care professionals is, in many cases, also a barrier to caring for adolescents. Many clinicians focus on the physical sequelae of adolescent health issues while ignoring the underlying environmental factors and health risk behaviors that lead to or are responsible for the conditions they see.[6] Visits to a physician for preventive care tend to be relatively infrequent and rarely include time spent on health counseling or guidance. The adolescent's fear (real or perceived) of lack of confidentiality, and a reluctance to share such intimate concerns as sexuality or family planning issues, substance abuse, and depression with their families and health care professionals create additional barriers to care. Finally, further barriers result from an inability to identify many of their own risk-taking behaviors as serious health problems for which they should be receiving counseling or care.

The preventable health problems of adolescents make the availability and visibility of preventive services critically important, particularly mental health counseling and reproductive health services, including the diagnosis and treatment of STDs and HIV infection. Because adolescents usually do not anticipate or plan for their health needs, multiple entry points into care are needed, as well as a sufficient diversity of confidential care resources.[7]

School-Based Health Centers—Developing an Appropriate Response to Adolescent Health Needs

The school-based health center model has proved to be a viable approach for providing needed physical and mental health care to youth, as well as for increasing access to primary care services for adolescent males and females. Most SBHCs have been established in schools where the student body is for the most part low-income, uninsured, or underinsured.

The range of primary care services provided by SBHCs includes physical assessments, long-term illness management, diagnosis and treatment of minor injuries, gynecologic examinations, immunizations, birth control examinations, family life education, prescriptions and supplies, laboratory tests, prenatal care referrals, STD diagnosis and treatment, family counseling, psychosocial counseling, parenting education, and weight reduction programs. Classroom health promotion activities and referrals to community agencies (with follow-up) are also commonly available.

Most SBHCs require signed parental consent before services can be offered to the student. Although this allows parents to exclude any services they do not want their children to receive, fewer than 10% of parents actually choose to exercise this prerogative for any of the services listed above.[8]

Reproductive health services in SBHCs range from programs that dispense contraceptives directly on campus to programs that offer written prescriptions (which are generally filled off campus by arrangement with a nearby pharmacy or clinic).

A relatively small proportion of student visits to SBHCs are for reproductive and sexual health needs. Nationally, the figure for such visits is 18.5% of all SBHC visits, compared to 26% for preventive care and 31% for acute care.[8] Nationally, only 25% of the SBHCs that serve middle- or high-school-age students provide on-site contraceptive services, although a slightly larger number (30%) dispense condoms. Research indicates, however, that effective contraceptive use among SBHC users is not necessarily related to whether contraceptives are dispensed on site, but rather to the number and frequency of contacts the student has had with a family planning provider. This is clearly an advantage of on-campus programs over other community and hospital-based clinics.[9]

Services at SBHCs are provided free of charge or at minimum cost. Nationally, the median budget for SBHCs in 1993 was $123,500; the median budget per health center enrollee was $196, with a median cost per visit of $71. These visits range from primary care visits to mental health counseling and treatment of ongoing health problems. In comparison, the costs associated with preventive services only (e.g., health screenings) range from $57 to $130 per adolescent per year in a fee-for-service system and from $72 to $172 per adolescent per year in a capitated system.[4,8] On average, 58% of eligible students in the school enroll for SBHC services; of those enrolled, more than 72% actually use health center services and make an average of two visits per year to the center for care.

Without SBHCs, many adolescents who are not covered by private insurance or Medicaid would not receive health services. For example, in New York an estimated 58% of students treated in 122 SBHCs are uninsured, a reflection of the fact that most SBHCs are located in poor neighborhoods.[8]

The advantages of SBHCs are that, for adolescents enrolled in school, the center provides ready access, does not require an adolescent or a parent to miss school or work for the student to receive services, and can respond to a broader range of needs (for example, both physical and mental health services) in one visit. The disadvantages of SBHCs include their limited availability outside of school hours and during the summer and the fiscal, administrative, and staffing challenges inherent in maintaining an on-site service delivery system that is geographically separated from the parent institution or agency that sponsors the facility. Overall, the ability to provide confidential services has been shown to be key to the success of SBHCs.[10]

Adolescents' Experience With Managed Care

Given the changing fiscal and service delivery landscape in the health care industry, various questions have been raised regarding the potential impact of these changes on adolescents: In light of the specific service needs of adolescents, are managed care systems able to deliver effectively and to coordinate the array of physical and psychosocial services adolescents may need? Do they make services available in the settings most likely to be used by adolescents? Do their provider networks afford access to professionals with expertise and interest in serving this population? There is also concern that, by imposing restrictive medical necessity criteria on the delivery of services, managed care programs limit reimbursement for mental health and other services far more strictly than they do for physical health needs.[11] As a result, drug and substance abuse treatment, reproductive health counseling, and nutrition counseling may be severely restricted or unavailable.

Because adolescent health problems are often a complex interrelation of diverse factors and are not strictly or solely physical in nature, diagnosis can be difficult or delayed if constituent causes or conditions must be dealt with at different sites or through multiple health delivery

systems. In addition, the flux in enrollment status within a managed care system, over which the adolescent has no control, may also interrupt or negate treatment efforts. Finally, the effect of these and other potential barriers to care is compounded in many cases by the adolescent's general confusion about how the managed care plan operates.

Little research is available that might shed light on the experience of adolescents in managed care arrangements or that compares the utilization patterns of adolescents who are enrolled in a managed care program or alternative system with SBHC use patterns. Thus, we are unable to ascertain whether SBHC and managed care systems are being used in a complementary or duplicative manner. Although studies of preadolescent children enrolled in Medicaid managed care plans suggest that they use preventive and primary care services chiefly for physical acute care or emergency care, the service utilization patterns exhibited by adolescents who use managed care systems have not been examined.[12]

The results of a study comparing utilization patterns of adolescents who use both a school-based health center and a hospital-based pediatric clinic showed that the SBHC was used more for counseling and health care maintenance, whereas the pediatric service was used for short-term and long-term illness.[13] In another study comparing SBHC utilization patterns by insurance status, students enrolled in an HMO demonstrated the highest rate of SBHC use and students without health insurance the lowest. Most used the SBHCs regardless of whether they already had financial access to medical care elsewhere.[1]

School-based health centers have long recognized that the lack of formal or informal agreements with managed care providers results in a de facto partial subsidy to the managed care provider for SBHC services provided to adolescents who also have managed care health coverage. In addition, the lack of a coordinated system of communication, concerns about confidentiality in sharing information between systems, and the minimal ability of SBHCs to collect financial reimbursement for services delivered hamper effective communication and cooperation between school-based and managed care systems.

From their perspective, SBHC staffs believe that many managed care providers have not made a serious effort to respond to the special needs of adolescents. Adolescents with managed care coverage do not always know to how use the system. They may carry membership cards in their wallets but may not know where the medical facility is located or how to access appropriate services. Parents do not always explain available health coverage to their children. When adolescents do attempt to receive care, waiting lists can be long for routine health care in managed care settings, sometimes with delays of as much as six weeks for a routine appointment.

When other potential obstacles are considered, the reasons become clear why an adolescent will often choose the SBHC over his or her managed care provider. Such barriers may include the adolescent's fear that records of the visit may not be kept confidential (an anxiety that may be particularly severe if the visit concerns a sensitive medical problem that the adolescent may not wish to discuss with parents); the financial burden of HMO co-payment requirements, which neither parent nor child may be willing or able to cover; or the time parents must take out of their work day to accompany their child to a medical appointment. The sheer convenience of the SBHC should not be underestimated as a notable factor in its use.

From the perspective of many managed care providers, however, important steps are being taken to improve delivery of care to adolescents. Special services are being offered for pregnant or parenting teens in a number of sites, and some managed care programs have established special teen health clinics for adolescent patients who are no longer appropriately served by pediatric facilities. Nonetheless, only a few managed care providers have developed programs to serve teens with special physical or mental health needs or made efforts to improve the quality of preventive health care furnished to adolescents by regular primary care providers.[11] One managed care provider that has made such efforts is the Group Health Cooperative of Puget Sound, Washington, which operates an adolescent center that serves as a referral resource for teens with emotional, behavioral, or substance abuse problems. In Spokane, Washington, Group Health Northwest operates a teen line to provide adolescents with access to a consulting nurse for information on a variety of health topics. Group Health Northwest also has a birth control case management program, in which nurses track and follow up referrals made for adolescents who are known to be sexually active to encourage and facilitate their continued use of birth control. In more than ten Kaiser Permanente HMOs in northern and southern California, special teen health clinics have been established to serve adolescent members in a separate, confidential clinic. These promising examples all point to the ability of managed care systems to respond to the needs of their beneficiaries in important ways, especially if up-front investments in primary prevention and early intervention are viewed as cost effective.[14]

Coordinating School-Based Health Centers and Managed Care Providers

To achieve a viable level of coordination and avoid service duplication between SBHCs and managed care providers, some communities across the country are exploring the steps needed to link these two service delivery systems. To accomplish this coordination, decision makers must understand the nature and value of school-based systems of care and recognize that these alternative delivery models do not merely duplicate services.

Confidentiality and information-sharing issues, reimbursement procedures, and formal coordination mechanisms are core issues that must be resolved before coordinated linkages can become fully operational. To ensure that patient information can be exchanged, a formal pro-

cedure must be based on consent forms signed by students and their families. Students should be assured that patient information will be kept confidential, which may be particularly problematic when adolescents wish to keep certain medical treatments completely confidential from all others, including their parents. They may fear that their medical records will not be kept confidential when the SBHC claims reimbursement from the managed care provider for certain sensitive services. These fears are not without justification. Many managed care providers will have to alter their current policies of mailing a notification of services received to the adolescent's home. Unless these and similar issues are satisfactorily addressed, SBHC providers may be reluctant to coordinate services with managed care providers.

Service and billing coordination also affects continuity of care and, thus, the quality of care adolescent patients may receive. Duplication of services or even duplication of payment can also occur when students receive care from more than one health care system. For example, if students who use SBHC services are also covered by a Medicaid managed care program with capitated rates, the state Medicaid agency is already paying for services for that student. At the present time, some SBHCs are billing state Medicaid offices under other funding streams apart from the Medicaid managed care program. In essence, therefore, the state is paying twice for the same patient. These systems will likely be eliminated in the near future. One result of system coordination, however, may be a strong sense of competition between SBHCs and Medicaid care plans if part of the Medicaid capitation rate is diverted to reimburse school-based health centers for services that are shown not to be covered by Medicaid or currently provided by the plan, leading to a reduction in payments to Medicaid managed care providers.

Accurate utilization and cost data, as well as appropriate administrative and management structures, are essential if SBHCs are to successfully provide cost-effective services within the reimbursement limits agreed to in contracts established with Medicaid managed care systems.[15] Another issue is the desirability of assessing the relative efficacy of both the SBHC and managed care models of care in terms of their ability to improve the overall health status of their adolescent clients. Although access to school-based and community clinic-based family planning services, treatment provided for STDs, and substance abuse health education efforts have been shown to decrease adolescent morbidity, further outcome studies are needed to ascertain the relative effectiveness of SBHCs and managed care providers.[16,18]

School-based health clinics will probably be able to operate as both capitated primary care providers and specialty providers for adolescent services. This will mean collecting capitated reimbursements and fee-for-service payments, both of which must be tracked and allocated according to service utilization trends. Each school-based health clinic may also choose to be either a direct contractor with the managed care program or a subcontractor to a community-based clinic or other provider of managed care services. One particular challenge SBHCs must address in devising any coordination plan is the fact that a school's students may participate in several managed care plans, each of which would require separate contract negotiations and service contracts. It may also be easier for a managed care provider to subcontract to the SBHC for adolescent services if it cannot offer a fully developed and comprehensive set of them within the main primary care site. This option may be more appealing to new HMOs that may not have invested as much in their initial infrastructure, compared to more established managed care programs, which could be more concerned about possible duplication of services.

Regardless of how or when adolescent services are provided, a clear arrangement for backup coverage outside the SBHC's operating hours, as well as coverage for hospital stays, is essential. Other issues include developing a capitated or fee-for-service system that would encompass both physical and mental health services and the need and ability to track students' use of the system while maintaining confidentiality.

Managed care contracts are based on risk-sharing arrangements designed to give primary care providers and other institutional providers, such as hospitals and specialists, incentives to work together to provide cost-effective care. At the present time, school-based health centers have had little, if any, experience with such risk-sharing arrangements. The SBHC must therefore be careful to negotiate a managed care contract that does not result in untenable risk.[10]

The needs of Medicaid-eligible SBHC users, the population upon which capitation amounts would be based, comprise a critical part of this analysis as well. If the number or proportion of SBHC users to be included in the capitated program is not sufficient to generate adequate reimbursement revenue to cover the operating costs of the managed care contract, little incentive would exist for the managed care program to participate. On the other hand, if most students at the school were covered under the same insurance plan, thus, in effect, creating a school-wide managed care system that covers primary care services, then billing the managed care program for SBHC services might become more manageable and cost effective. In this case, responsibility for secondary and tertiary care would still need to be arranged.

Perhaps the most challenging barrier to coordination pertains to financing, as both SBHC and managed care models compete for a limited amount of funds. Although managed care providers may support the concept of increasing access to care through school-based models, a disincentive to forge coordination agreements nevertheless exists, because it may well mean giving up some funds at a time when competition for the medical dollar is fierce. In addition, SBHCs may be perceived as a potential source of added cost to the managed care system as they attempt to increase the number of visits and

services they offer to students. Developing viable relationships between managed care and SBHC systems requires agreement on who will be responsible for providing what array of services, where the services will be delivered, and who will pay for these services.

Because managed care providers are liable for their enrollees, legal issues also enter the picture. Under an agreement of coordination, if the SBHC provides care to managed care clients, the managed care provider will need to oversee the SBHC to ensure quality of care.

Potential Models for Coordination Between Managed Care Systems and School-Based Health Centers

Despite the obstacles that lie in the path of successful coordination between school-based health centers and managed care providers, several promising approaches are emerging that can help to close the gap between these different models of care. State governments are in the early stages of determining the appropriate relationship between SBHCs and state-sponsored managed care programs (many of which are under the auspices of state Medicaid programs). With an eye toward reining in health care costs, reducing unnecessary care, and improving access to preventive services, states are establishing managed care networks to regulate the health care consumption of Medicaid recipients. For the most part, SBHC managed care relationships are being developed at the community level. Individual school-based health centers or their parent institutions are attempting to negotiate agreements with managed care providers concerning services to be provided to managed care enrollees, as well as reimbursement mechanisms.[11]

In some instances, SBHCs have joined managed care provider networks and share in the primary care capitation payments; other SBHCs have established a reimbursement relationship that covers only specified services delivered to the managed care provider's patients; in still other cases, no relationship has been established. A recent survey documented only limited coordination and negotiations between SBHCs and Medicaid managed care programs.[10] This was attributable to either the small number of SBHCs in the state or the absence of Medicaid managed care programs, or both. States with more extensive Medicaid managed care and SBHC activity have been more likely to explore facilitating relationships by either encouraging or even requiring formal arrangements between the two.

At the state policy and community levels, Medicaid managed care providers in St. Paul, Minneapolis, Baltimore, and San Francisco and in the states of Oregon and Rhode Island are beginning to coordinate their efforts with SBHCs. For example, state agencies are mandating that managed care programs and SBHCs, among other organizations, develop agreements that authorize payment from the managed care plan to the providers of such services as immunizations and treatment for STDs and other communicable diseases. They are also required at a minimum to coordinate service delivery with SBHCs as a condition for participating in the Medicaid managed care program.

Another approach has been the development of legal contracts, including fee-for-service reimbursement, between managed care plans and SBHCs. The contracts treat the SBHC much like any other plan provider, and physicians are subject to review for quality standards as are other providers in the managed care system.

Another model has been the development of formal protocols for referral and treatment between managed care providers and SBHCs. For example, some managed care providers have worked out a detailed agreement with local SBHCs to coordinate services for students who are enrolled in both systems. These protocols detail when it is appropriate for the SBHC to provide services and when a student should be referred to the managed care facility. When students receive on-site care at a school-based health center, the SBHC is reimbursed at Medicaid rates. The SBHC is required to report to the students' primary care physicians information on services provided so that the physicians stay informed. Follow-up appointments are often scheduled with the primary care physicians.

At some sites, managed care providers are participating in coalitions that fund and develop SBHCs. For example, Medica, a managed care plan in Minneapolis, is underwriting the full cost of an SBHC for a year. The other managed care plans in the county are also collaborating and have pledged $1 million to fund other SBHCs. In other communities, managed care programs directly administer SBHCs. In this arrangement, a patient data system is developed so that when a student receives care at a school site, the record of that visit is available throughout the managed care computer network in case the student seeks care at any of the participating sites.

In some communities, the managed care provider authorizes the SBHC to provide care and bill Medicaid directly for services. In this coordinated approach, SBHCs are designated a Medicaid authorization number from a managed care provider to treat students and bill Medicaid directly. For example, primary care case managers will authorize the SBHC to conduct comprehensive health screenings for managed care enrollees. One managed care provider has authorized a school-based health center in an alternative school for pregnant teens to deliver all prenatal and postpartum care to several of the plan's Medicaid-eligible members.

Another level of coordination and referral between managed care systems and SBHCs is reflected in settings where managed care providers offer expedited appointments when the SBHC refers students to the managed care provider. When a patient enrolled in the local managed care system is seen at an SBHC but needs further care, the SBHC arranges a speedy appointment. Essentially, the SBHC performs a triage function, making referrals by assessing the urgency of the problem. This screening and referral service is not currently reimbursed by the managed care program, however.[14]

As indicated by these examples, a variety of approaches can be used to create formal relationships between managed care providers and SBHCs. Little has been done in most states to regulate or influence the relationship between SBHCs and the state's Medicaid managed care plan, however, leaving negotiations essentially in the hands of individual SBHCs and local managed care providers. Thus far, many school-based health centers have found this to be an intensive process that often overtaxes an already overextended staff.

Summary

Within the arena of adolescent health care, the most critical service delivery issue is access to care. Efforts to contain health care expenditures through managed care plans inevitably conflict with efforts to deliver truly comprehensive preventive services to all adolescents. Because of the substantial increase in risk behaviors, prevention efforts require frequent contacts if interventions are to be made before risk behaviors occur or soon after their onset. In addition, yearly screening for all adolescents is likely to identify many teens who could benefit from early interventions. Enabling school-based health centers to provide services in coordination with managed care systems would go far to ensure access to care, as well as appropriate attention to the special needs of adolescents, in a timely and cost-effective way. Furthermore, that access would not be tied solely to the family's choice of provider or to the provider mandated by the adolescent's insurance plan.

Underlying any approach to coordination of services, however, is the need for managed care providers to understand and affirm a preventive care investment in young people as a means of reducing health care expenditures, an investment that would pay dividends not only during the adolescent years but into adulthood as well.

Whether the willingness exists to make this investment, when the cost savings may not directly accrue to the adolescent's current HMO, presents a conflict between the present interests of the HMO and the future interests of whatever provider the adolescent sees as an adult. As managed care systems are more widely adopted, it will be important to ensure that they adequately incorporate the service delivery components that have been found to be efficacious in serving adolescents. Given the leading role school-based health centers can play in providing preventive health care and health promotion, managed care providers should be encouraged to develop strong partnerships with such centers, so that the dual goals of high-quality care and cost containment can be achieved.

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Reproductive Health Practices of HMOs Serving Urban Low-Income Women

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As managed competition expands, many health plans wish to open their membership to those on Medicaid, mostly women and children. This study examines the reproductive services of 10 diverse managed care organizations historically targeting large numbers of poor women for care through prepaid Medicaid contracts. These institutions think themselves united and unique within managed care because of their long-term commitment to serving patients on Medicaid. Although the interviews with providers and administrators explore many aspects of reproductive care, most of these health maintenance organizations (HMOs), by the nature of their funding and federal mandates, have more aggressive and defined programs for pregnant women and for infants. These urban-based providers have discovered by trial and error the challenges of getting quality health care to poor women: external administrative or bureaucratic challenges because of Medicaid, internal administrative or provider barriers, and the artifacts of patient behavior. Strategies to address these problems involve attending to political and bureaucratic factors affecting care, taking a broader social view of patients and their community, using community resources to supplement HMO benefits, maximizing each contact with patients with multiple interventions, case management to monitor underutilization, aggressive outreach, service, and follow-up.

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Health care is evolving toward managed care as the standard for Americans. Enrollment of middle-class and working-class persons in health maintenance organizations (HMOs) and other prepaid systems is growing rapidly. Beneficiaries of state-funded programs, Medicaid and Medicare, are increasingly offered this option as well.[1] Studies indicating that minorities are less informed than whites about available health services in their communities and how to use them suggest that these groups may be less effective consumers of managed care.[2] Thus, the processes of integrating socially diverse patients into these systems, ensuring that the poor and persons with special needs receive adequate attention, addressing barriers to care that may continue to exist, and controlling costs are critical issues in health care reform.[2-4] In fact, debate continues about whether managed care can be broadly implemented.[5]

Scope of the Problem

Women's reproductive health services highlight the challenges of extending managed care to the urban poor, in part because women use substantially more health services than do men, particularly during their reproductive years. Furthermore, since April 1990, federal legislation has mandated that Medicaid cover all pregnant women who are either at or below 133% of the poverty level for up to 60 days postpartum and some states exercise their option of including women up to 185% of the poverty level.[6,7]

Pregnancy is the only time poor, adult women who are not elderly, disabled, or parenting a child under 18 years of age have full access to Medicaid,[7] reinforcing messages to poor women that the health of their baby is the prime concern of the health care system.[8] Medicaid typically exceeds private insurance in its expanded coverage of nutritional and substance abuse counseling for pregnant women.[7] Still, pregnant women on Medicaid are frequently denied care.[9] Obstetricians have the highest rate of refusal of Medicaid patients of any specialty and in more than a quarter of the counties in the United States no prenatal clinics serve Medicaid patients.[7] Bowley found that 67% of drug treatment programs in New York City rejected pregnant Medicaid recipients, and 87% refused the women if they were also crack-addicted.[8] In response to this need, managed care systems arose around the country especially willing to enroll such patients. Several of these HMOs grew out of community clinics that had served the same populations for decades. Poor management led to the closing of many plans, but sound, committed groups survived and were joined in the marketplace by other community-based managed care programs. Most recently larger, more mainstream HMOs have also been exploring adding Medicaid populations to their membership.

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ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
HMO = health maintenance organization
IPA = individual practice association
PPO = preferred provider organization
TAB = therapeutic abortion

The intent of my qualitative study was to explore the challenges and strategies organizations have uncovered in the course of their service to this group. The study uses a convenience sample; thus, it is not representative of all HMOs serving poor, urban women or of all women on Medicaid. My intent is to illustrate, using ethnographic methods, examples of structural and social dilemmas posed and insights gained in these care settings.

Methods

Semi-structured interviews were conducted with 24 persons: chief executive officers, medical directors, chiefs of reproductive or maternal health services, and other key persons in HMOs that have sustained services to poor women of color and that serve a majority of their patients through prepaid Medicaid contracts. The sample came from the membership of the National Association of Urban-based Health Maintenance Organizations, a small group of predominantly minority-owned or managed health centers in existence for as long as 26 years. Chief executive officers of each organization were the first persons interviewed, and they then identified their key personnel in reproductive services and policy. No program refused to participate; however, scheduling difficulties resulted in incomplete contacts with two agencies, leaving a total of ten organizations included in the results.

The telephone interviews lasted one to two hours. Two site visits on the East and West Coasts included observations of health centers as well as face-to-face interviews. A previous literature search had retrieved little information on reproductive services to this group in managed care settings, but suggested critical issues for exploration, as did preliminary discussions with providers.

The interview schedule was designed to illicit information on the nature of services: the history of the health center; the scope of reproductive care offered to Medicaid-enrolled patients; restrictions to benefits; types of service locales; special needs of the population; challenges to providing care; techniques and strategies; a description of staff providing reproductive care; outreach and enabling services available; and collaborative relationships within the community. In addition, respondents shared relevant service and population statistics to frame their discussions.

Sorting and coding of the interviews uncovered patterns of response, themes in treatment, and critical paths for further analysis. Dissemination of individual interview summaries (not identified by contributor) and of the preliminary analysis to the respondents and other reproductive care providers both in the participating HMOs and elsewhere assisted with measurement of the validity of the qualitative data.

Organizations in the Sample

The health plans were diverse; only a few of these HMOs have Medicaid contracts covering 100% of their patients, but all have at least 60% of prepaid Medicaid patients in their membership. The average number of such members among the sample is 82.4%; the largest serves about 130,000 low-income patients, a second group cluster serves between 72,000 to 50,000, and the smallest have 33,000 to 25,000 members. Three organizations have substantial numbers of Latino patients and the rest serve predominantly African-American women and children, with a few white patients as well. The number of male members is small in these plans, and little to no reproductive care is specifically targeted toward men.

Within this context is every form of managed care: staff or group models, contracted services through preferred provider organizations (PPOs) or individual practice associations (IPAs), structures incorporating several health delivery models, often including poor, fee-for-service patients as well. All services are offered in the low-income communities in which their members live, though this area can be quite large.

Plans offer a broad range of contraceptive supplies and services through a primary care physician, and gynecologists are considered specialists seen only on referral or during and immediately after pregnancy. Providers recommend birth control methods based upon their assessment of the social, economic, educational, and emotional resources of the patients. For instance, Norplant is no longer in favor with these plans because of the cost, side effects, or poor patient satisfaction. Family planning counseling has been eliminated from most Medicaid contracts, and infertility services, always controversial among these providers, are rarely offered. Sterilization is usually available, though reversals are not; state laws on abortion affect the accessibility of this procedure, but it is a benefit in most plans. Routine gynecologic examinations, screenings for breast and cervical cancers, or diagnosis and treatment of sexually transmitted diseases and human immunodeficiency virus (HIV) are also typically available in these plans, but are less well defined and may vary notably in scope, reflecting, in part, primary care physicians' sensitivity as well as the availability of these services in other agencies in their communities.

The number of deliveries in the sample ranges from a high of 415/1,000 per year to the lowest, 17/1,000. That higher number, however, is a dramatic outlier; without it the average number of deliveries among the group is 40/1,000. The large number of high-risk deliveries requires that all of these health centers invest heavily in comprehensive prenatal and early postnatal care, including the allocation of substantial resources to outcome management—social interventions designed to reinforce positive medical outcomes such as postpartum support groups to discuss emotional issues, nutrition and

dietary services, residential or long-term outpatient drug treatment, home visits, and referrals to other resources throughout the community.

Challenges to Care

Patient satisfaction surveys find that Medicaid-enrolled members are overwhelmingly pleased with managed care; however, challenges remain to high-quality reproductive services from each constituency—the state bureaucracy, providers, and the patients themselves.

Respondents' attitudes toward each challenge include frustration, resignation, acceptance, empathy and the belief of one medical director, "Don't curse the darkness; celebrate it." Regardless, they all have learned that such issues present the framework around which expanded models of managed care will take shape. These respondents think their plans are demonstrations of the potential for putting medical service models into operation for poor women on a larger scale, and they express considerable cynicism about the willingness and capacity of "mainstream" HMOs to handle the array of challenges presented by a service commitment to these patients.

State requirements and restrictions affect the scope of reproductive health services. A 1987 statute ensures that Medicaid enrollees, unlike other members, have full freedom of choice of family planning providers in order to offset potential limitations within a plan.[7] Thus, if a member goes to another health center, such as Planned Parenthood, for reproductive care, the plan must pay. Reimbursement rates and eligibility criteria for screenings of breast and cervical cancers vary widely by state, as does the frequency of authorization for such services. In addition, any or all of these elements can change with a new state contract.[7]

Though the Hyde amendment has limited the use of federal funding of abortion since 1981, California places no limit on the number of abortions available to patients, and abortions can be done up to 24 weeks into a pregnancy. If no physician in the area does abortions that late in a pregnancy, a patient is sent to another locale at a cost to the plan. In other states, however, Medicaid members are paying out of pocket for the service. One plan found that it was not even in control of the availability of contraceptive methods because of the nature of billing, exclusions, and reimbursements. Neither sterilization, over-the-counter contraceptive methods, nor family planning visits were covered in their contract. Even when a reproductive service is a benefit, follow-up care may not be reimbursed, as in the case of a woman who could receive genetic counseling, but was refused authorization for care of her encephalic child.

Medical providers may also find that services they once relied on to best treat their patients are no longer available through prepaid Medicaid benefits. Treatment for mental illness and substance abuse has been eliminated in several state contracts despite the high incidence of these problems and the cost of medical care to women and children as a consequence. In another state, social work services are also no longer covered and HIV-nurse case management is being threatened. The changing benefit packages determined outside the plans themselves are often confusing for everyone—providers, administrators, and patients. Patients who do not understand the loss of services they once had accuse the plans of withholding care. External problems can retard service delivery, challenging relationships with providers as well as patient care. One HMO had three providers refuse to do family planning because of past rejection of their claims and their inability to manage care as they wanted.

Open enrollment required for Medicaid patients and changing eligibility rules are another source of flux in these settings, impeding continuity of care. Enrollees may leave a plan when they move out of a service area (sometimes only a matter of blocks from their original address) or because they do not understand and are frustrated by the rules of an HMO.

As one medical director said, "The problem is the bureaucrats don't understand managed care." State Medicaid systems have medical templates beyond fee-for-service for serving this group and these processes may not translate well into managed care in part because of the challenges these patients bring to their care. State bureaucracies have different levels of appreciation of the function of managed care sometimes even from one administration to the next and several respondents reported that state Medicaid officials are anxious to support care in these settings and to find a way through administrative problems. Nevertheless, a plan's success serving this population in part depends upon its sensitivity to the shifting administrative and political issues that affect the care of their women patients and on identifying opportunities to educate state officials on the practices of these emergent models.

Challenges for Patients

Respondents' discussions of medical issues are always interwoven with social analysis. In varying terms, they all assert that adapting to the needs and characteristics of patients on Medicaid makes all reproductive health care, to some degree, social intervention. Medicaid patients are diverse; thus, respondents frequently express concern about creating stereotypes of the attitudes and behaviors of poor women. The same psychosocial issues are mentioned repeatedly as central challenges to developing effective managed health care for these patients, however: coexisting medical conditions such as gestational diabetes mellitus, high blood pressure, or addictions; complicated compliance issues and delays in prenatal care exacerbated by patient mobility and turnover in enrollment; the unnecessary use of emergency and ambulance services; the large number of adolescents having intercourse without contraception; and an unacceptably high rate of repeat abortions. For all these reasons, based upon American College of Obstetricians and Gynecologists' standards, most respondents thought that most obstetrics practiced in their managed care settings was "high-risk."

Other studies have found that African-American women have a lower incidence of breast cancer than white women[10]; yet several plans have noted more cases of this disease including among women under 45 than is described in the literature. Therefore, they have decided to maintain conservative screening standards. One group with a high AFDC [Aid to Families with Dependent Children] membership has uncovered 12 cases over the past year; most were women younger than age 35 and two were pregnant at the time.

Sick or abandoned babies, or both, born to drug-addicted mothers are a problem for several plans. A medical director stated, "We [in managed care] are all motivated to avoid the $250,000 baby." Indeed, one HMO delivered a premature child in June who by October had cost $200,000 and was still sick; by that time, the mother had disappeared. One HMO sees an average of six "boarder babies" (babies living long-term in a hospital because the mothers either have abandoned or are unable to care for them) at any time, most of whom were born 1 to 3 months premature with complications to mothers who had no or little prenatal care and were involved with drugs. One respondent who had collected data found that the incidence of drug-related complications among Medicaid deliveries in his plan was lower than among the fee-for-service poor patients.

Noncompliance is a substantial impediment to service delivery. Lack of formal medical care is seen as a multigenerational habit. Furthermore, "[The patients] have other stresses and this [medical care] is not a priority." Other respondents acknowledge that compliance problems can be generated by institutional paternalism or chaos.

Despite many creative health education initiatives, no plan is satisfied that they are getting to women who do not make early prenatal visits. Between 17% and 30% of pregnant women in these settings do not receive prenatal care until their third trimester. Denial of possible problems is a universally noted obstacle. Delays in prenatal care can be caused by a combination of factors, however. Under some HMO procedures, once a woman misses a period, it can take weeks to get an appointment with her primary care provider who must refer her to an obstetrician; at that point it may be difficult to locate her if she has moved or does not have a phone. Thus, by the time a woman is actually scheduled for a prenatal visit with an obstetrician, she can already be well into the second trimester.

High patient mobility is another serious service access problem mentioned repeatedly. Though women must have an address to enroll, it is not unusual to learn a patient has relocated even within the 30-day enrollment period. Many poor members are transient or even homeless, at least for short periods of time. Respondents in two different plans identified pregnancy and the period just after delivery as times of increased risk of shifting residence as women move between their parents' and boyfriends' or husbands' homes. Frequent moves can mean a patient does not know how to get to the clinic from her new address, may not trust neighbors enough to leave her apartment empty, or does not know anyone in the neighborhood with whom to leave her children during her medical appointment. Many poor women have no telephone and communicate entirely through beepers and public phones. Both patient mobility and the turnover caused by changing enrollment and eligibility make it especially difficult to teach patients the best and most appropriate use of services.

Although patients receive orientation, respondents agreed that they need in-depth education on using the system. As the medical director of a larger HMO stated,

> The population has been rewarded by clinic-based services for poor help-seeking behavior. . . . Patients have found there are no negative consequences to waiting until the last minute. They can always be seen [in most emergency departments], so when we come in wanting to provide timely care, we bump up against the other [models and experiences better known to the patient]. . . . Fee-for-service asks for less discipline from patients. When she joins the HMO, she is often unhappy with the demands placed upon her for discipline.

Two plans that have compared utilization rates among patients in their clinics found the inappropriate emergency department use of Medicaid members lower than in the fee-for-service patients, however. These findings suggest that efforts at educating poor women to the culture of managed care can be successful with time and patience.

Sex without contraception, pregnancies, and deliveries among teenage girls are also serious challenges for every plan reporting, such that each has had to actively determine the allocation of resources they will make to teenaged pregnancy prevention and care. Of the Medicaid membership of one HMO, 65% are boys and girls under the age of 16 and "their knowledge of birth control is abysmal." A local university found that by the 12th grade 75% of boys and 65% of girls in their service communities are sexually active, 10% to 20% by the 9th grade. That plan has treated pregnant 11-year-old girls. Thus, providers of obstetric-gynecologic care in these HMOs must have greater sensitivity to children to understand how, as one respondent stated it, their concrete thinking obstructs history taking. She illustrated the point by describing a patient who when asked by a provider whether she was ever sexually active responded "no" because, she explained later, she just lies there.

All the plans complain of high rates of multiple therapeutic abortions (TAB) among the members. One HMO has done 1,400 TABs in the past 9 months, and the average time between abortions for women in several plans is 6 to 7 months. Another respondent noted that teenaged girls in her plan are likely to use repeat abortions as contraception despite intervention. Ineffective contraception and repeat abortions are not isolated to teenagers, however—the average age of women engaged in these behaviors is the middle to late 20s. "We have fallen short for these women. We just haven't addressed their reality. Something leaves them vulnerable." Another obstetrician-gynecologist saw the problem in terms of the limitations of birth control methods themselves and the lack of "user friendly" ones for poor women. But some respondents thought

elements of their managed care model itself may hamper change. Typically, a woman seeking a TAB, for instance, is disconnected from her primary care physician because the service is offered in specialized medicine or in contracted centers (like Planned Parenthood) away from the HMO.

Issues for Providers and Models of Managed Care

Contracted providers sometimes work with many plans and, therefore, do not necessarily know all the obstetric and gynecologic benefits available to members. Although this situation affects "mainstream" managed care institutions with network models as well, the number of Medicaid regulations, changing eligibility, and the low education level of the women who are themselves not always aware of their benefits package, put somewhat more pressure on these providers.

Most small medical offices in a network cannot accommodate services like child care even if they are essential for the delivery of women's health services. Physicians in a group have the advantage of easier access to ancillary services for their patients like referral, outreach, case management, dietary assistance, and social workers. On the other hand, one manager who has both staff and IPA models in her plan said, "We ask things of the [staff] HMO doctors that we do not of private doctors who are not being monitored. While the care may be good [among contractors] because we chose them, it is not up to the standards of care of the organized medical setting." Though it is important for network-based programs to facilitate equal access to patient resources and equal expectations of care, few have that ability at this time and three of these plans are moving toward staff-based service models.

The number of social challenges to reproductive health care delivery makes these plans keenly aware of the cost of physicians' time. Respondents thought that if a psychosocial program was already in place, their physicians would support and use it, but that like most physicians theirs could not be expected to spearhead such interventions. "I envision," a provider-manager said, "a program led by doctors, but not conducted by them. What is being asked of us in the name of quality, doctors don't do well anyway." Other plan managers thought that the shrinking allocation of the health care dollars would increasingly demand that they do more with less and most agreed that the answer to effective medical services for poor women in managed care is in the increased use of an array of "mid-level staff" such as nurses, dietitians, and social workers, focusing physicians' services on the truly ill. Such staff, when interviewed, stated that they would like to have direct access to the patients without having to go through a physician. Yet often the HMOs' insurance coverage prohibits the use of nurse practitioners as primary care providers.

Finally, respondents identified as a challenge for their plans the recruitment of providers who can manage cultural barriers to reproductive health care, such as the fear of acknowledging sexual experience observed among some young Latinas. Cities throughout the United States have a growing Southeast Asian population of women who appear uncomfortable using male physicians or getting breast examinations and have no history of receiving mammograms and pap smears or an acceptance of reproductive service. Yet there was debate among respondents about the need for cultural, racial, or gender matching of clients and providers. In the context of managed care, this task is compounded by the paucity of African-American, Hmong, Mien, or Latina physicians with whom to contract. In some places, once again, mid-level staff from backgrounds similar to patients are seen as an answer. Other solutions include:

- Aggressive solicitation of minority, bicultural, and women physicians;
- Identifying empathetic physicians of any race and gender;
- Provider education and monitoring on cultural issues;
- Multidisciplinary case management discussions in the context of treatment planning;
- Training peer educators in high volume clinics to work with women on child care information and health education;
- Recruiting providers who live or practice in the neighborhoods served; or,
- Composing a majority of the Board of Directors from consumers.

Most such plans cannot afford the level of education or support services they would like to give providers to help them handle the demands of serving women in such great need. Half of the administrators in the study define their role in the plan to encompass helping staff understand and accept their limitations and to focus the providers continually on what more than one medical director described as "the mission to serve."

Strategies for Enhancing Care

Anticipating state restrictions, being proactive about patient needs, hiring and supporting a diverse staff, and regular chart monitoring are critical elements in the success of these institutions. A distinguishing element in these HMOs is their belief that providing psychosocial interventions is central to delivering managed care to poor young women. These discussions typically go well beyond the issues normally raised by medical providers. Respondents frequently mentioned the need to teach their patients self-esteem and "who's important in the relationship" in the context of obstetric and gynecologic services. Comments included, "Until we start treating children as respected people, the pregnancies will continue" and "There is a link between sexuality and environmental violence." Another medical director said, as she described fourth-generation motherhood in a 12-year-old girl pregnant by a man who is now in jail, "Children who never see their parents go to work find it hard to not see absence of self-caring as normal." Still

another physician referred to "the mistrust factor" caused by social isolation that results in limited or hostile participation of these women in health care. Respondents agree that the standards of care as set by American College of Obstreticians and Gynecologists, the Public Health Services, and other monitoring agencies can be achieved, but require adaptation of managed care models. Flexibility in delivery of care, incentives, enabling services such as transportation or baby-sitting during medical visits, outreach, and case management are elements of every plan's reproductive care.

Strategies for Better Reproductive Service

Short-term incentives to motivate patients, although helpful, are not uniformly successful. For example, one plan gave a $25 incentive to one group of women and not another to encourage them to get mammograms. The providers found no difference in utilization between the two groups, but thought that it takes time for word to spread among members about incentives and for any change in behavior to take hold. Long-term or sequenced incentives like coupons toward baby care equipment given at each visit have been more effective because interest and motivation build over time. Similarly, expanded access strategies get varied results—most plans that extended hours of care found few women used the options; however, the immediate registration of women wherever they appear in the system and 24-hour phone availability of member services staff led to greater continuity of care.

Aggressive outreach is also a universal tool for these plans. In fact, one associate medical director insisted that it is impossible to meet the standards of the American College of Obstreticians and Gynecologists' Committee on Quality Assurance unless a plan is enterprising and even "pushy." The "big players [mainstream HMOs] don't know the level of outreach needed to work with this population of women." Several plans maintain their own outreach staff, but others work with programs in the community such as a "Mom-mobile" that identifies pregnant women for care.

Fostering relationships between patients within the health care setting is another important and effective strategy perhaps, as two respondents suggest, because so many women feel isolated and need social connections to motivate self-care. Events like baby showers are popular as are any group interventions that include food and fun. An obstetrics department chair described her goal as "developing relationships with women [within the HMO] in their own language, not talking down to them." One plan that uses older women not only as sitters but as mentors to their younger mothers has seen substantial health behavior change in both groups. Another plan launched an effort at reducing the delay of prenatal visits by intensifying relationships between pregnant women and female obstetrics department staff, and has seen first trimester appearances increase from 23% to 64% in three years. "Good medicine is not enough. A plan has to elevate people and that means dealing with social problems, having active involvement with patients in the face of state limitations."

Aligned with this view is the belief that their commitment to care requires them as institutions and individuals to be involved in their immediate community in ways they see as distinct from the behavior of staff in mainstream HMOs. Chief executive officers regularly spoke of their participation in neighborhood health planning groups, task forces, and boards of other community-based agencies; and their facilitation of services to women members even when the care is not covered as benefit.

Most plans further acknowledge a responsibility to the neighborhood they serve by creating activities for nonmembers, such as soliciting male partners of pregnant teenagers; locating general equivalency classes or food distribution programs on site; or, in one case, commissioning a community theater project to dramatize breast cancer prevention and treatment. Many plans have directed school-based or community-based interventions in which they review family life courses, collaborate on making health education materials available, do medical screenings, or, in a few places, actually provide contraception, teen parenting, and perinatal care on the school site.

Close relationships with schools are seen as an important source of early identification of pregnant teens for case management. Yet another plan has an adolescent program in development that would work with teens, pregnant or not, teaching them specifically about sexuality but also about abuse and the violence these children may experience that impedes good reproductive decisions.

Drug treatment is so critical to reproductive care that two HMOs have contracted with substance abuse programs around the area to add up to five long-term residences to their list of contractors in each plan for pregnant women. As a result, there is now never a wait in either plan for those patients who wish drug treatment and for the first time women with children have a residential treatment option.

Another plan has a major mental health component and provides substance abuse treatment in-house. A methadone program they began in 1987 uncovered numbers of pregnant women addicted to cocaine. At this time about 18% of deliveries are drug affected; their new program, "Free at Birth," is a response to this need. They provide support groups for up to the fourth week postpartum, as well as an integrated package of health education, social work, case management and obstetric care—all at one site, delivered on the same day. Most plans refer illicit drug users diagnosed by an obstetrician out of their plan because of the limitations or exclusions of their mental health services contracts with the states. This situation leads to problems with patient monitoring and integrated care.

A different plan found a solution in collaborative agreements allowing the placement of prenatal education within the treatment facility and transportation of patients to all medical appointments. Most addicted

women chose the day treatment option, however—7 days a week, 6 hours a day, for 6 months. Outpatient counseling 2 days a week is also available with day care for children.

One Strategy to Control Costs

As in any HMO, the cost of care is a concern, and these plans focus medical interventions, health education, and outreach efforts on this issue. The "OB on Call" schedule was developed by DC Chartered Health Plan as a result of many women presenting to deliver without previous care. In this system, most physicians agree to be on call seven days at a time to see women wherever they show up, even in a non-plan hospital. A physician on call may get anywhere from zero to ten calls during this time. If members are unregistered and medically stable, they will initiate a transfer to a plan hospital where they have obstetric privileges. The physician then notifies utilization management with a plan for care. If the woman is not stable enough for transfer, she will be delivered at a nonparticipating hospital by the physician on call. They have 80 to 90 deliveries a month and have 20 to 25 of these delivered by the obstetrician on call, generally in plan hospitals.

If a woman arrives at the obstetrician's and is visibly pregnant, the physician completes a registration form and the woman does not need a referral from her primary practitioner. The physician is paid for the first visit at a flat rate and then paid a global rate for the rest of the pregnancy care. The goal is for a minimum of nine visits during this time, but the average now is five. The global fee is based upon this assumption plus one postpartum visit. If women arrive at the emergency department or nonparticipating clinics, they are referred to the obstetricians on call who include them in their practice for the duration of the pregnancy.

These managed care systems have, by virtue of their many challenges and their long histories with the urban, poor women they serve, have had to link cost-containment with advocacy to survive. A respondent warns, "There is always a resource factor in a medical facility like this one—any plan serving this population has to be willing to accept a lower profit margin."

Summary

These medical centers would like to provide much more care. For instance, with a better-integrated database, one HMO with a high incidence of breast cancer in young women would like to be able to do early detection and follow-up on teens from families with histories of breast disease. In truth, these facilities elicit more history than they can address with their limited resources and small sizes. Therefore, they all employ four primary service tactics:

- They take advantage of as many existing community resources for referral or collaboration as possible;
- Opportunities to intervene with women in any setting are maximized;
- The provision of case management is considered basic to the effectiveness of reproductive care practice to poor women, so much so that two plans with IPAs require each office to provide a case manager onsite; and
- These plans all use what others might label intrusive measures: establishing a policy of offering women with histories of multiple abortions Depo-Provera shots; flagging pregnancy test results for follow-up by outreach staff; targeting a woman for education due to and access to names of people in her social network; bombarding drug-using women who are not participating in treatment with information, encouragement, or referral to other programs for follow-up even at the risk to confidentiality; or, the use of community health workers to seek absent patients in the streets, at home, or through contacting neighbors and friends.

They have demonstrated that effective care can be provided at controlled cost, that poor women can be partners in that care even in the face of great challenges, and that "plans serving the poor are not poor plans." Two studies of Medicaid patients suggest that enrollment in managed care may have a modest beneficial effect on the prenatal care received by the Medicaid population and that providing financial access and modifying the system of care for this population did not result in parity with the general population.[1] Careful quantitative and qualitative studies should be done in these urban-based plans to determine the effect of the various interventions on reproductive health. Without aggressive involvement in the social as well as medical aspects of reproductive health care, however, providers will see a new generation who are even more difficult and more expensive to treat.

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Health Plan Marketing and Reproductive Health Services

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Managed care organizations must differentiate themselves in a manner that is meaningful to the market if they are to prosper in an increasingly competitive marketplace. The use of reproductive health services to provide this differentiation can be examined by applying consumer behavior models. These models suggest that meaningful differentiation is likely to be provided by maternity and infertility services—high-involvement services for which differences between the competitors can be assessed in advance. Contraceptive and family planning services are generally low-involvement services, as well as being provided equally well by most competitors, providing little meaningful differentiation. Abortion, at the time of health plan selection, is likely to be a low-involvement service as well because most women do not anticipate needing an abortion until they are already pregnant; in addition, abortion, because of its politicized nature, is not a service that most health care organizations want to advertise. The patient-physician relationship is the one variable that managed-care organizations may be able to market across all reproductive and women's health services.

In their efforts to compete for customers in an increasingly competitive health care marketplace, managed care organizations have sought to differentiate themselves from their competitors. Not all forms of differentiation are meaningful to the consumer or the employer, nor are they desirable from the point of view of the managed-care organization. Yet these organizations must find ways to make themselves more attractive than their competitors to at least a segment of the market of consumers and employers; otherwise, their continued existence cannot be assured.

This article examines the role that reproductive health services can play in providing managed-care organizations a basis for differentiation. The services that will be considered include contraception and family planning, abortion, infertility services, and the full range of maternity services. From a marketing perspective, I explore what constitutes meaningful differentiation to the consumer and, to a lesser extent, to the employer. This requires heavy reliance on the field of consumer behavior and on established consumer behavior models.

Reasons for Joining a Managed-Care Organization

Studies in the marketing literature have been fairly consistent over the past 15 years in citing those factors considered by consumers to be most important in their selection of a managed-care plan. Broad coverage, lower costs, and guaranteed access to care have been the three key attributes necessary to attract members to managed-care organizations.[1]

The attributes that would deter consumers from joining a managed-care organization are the cessation of an ongoing physician-patient relationship, limited choice of providers, and the inconvenience of having to go to a centralized location to receive service.

The first two points address a key issue in health plan marketing—the acquisition or maintenance of a physician-patient relationship. The service marketing literature has increasingly recognized the primary importance of the relationship between the professional service provider and the client.[2,3] Private research in the health care area confirms this importance and is reflected in the advertising of many managed care plans. Typical are the advertisements of Pilgrim Health Plan in New England, which state that what matters may not be the 1,200 physicians they have to choose from but the fact that they have just one, implying that they have the one physician who is important to the consumer.

In the broad area of services defined as reproductive health, the physician-patient relationship presumably also plays a dominant role, assuming that the patient is in a setting where reproductive health services are provided by a known and trusted physician or other clinical professional. Interviews with managed-care marketing managers indicated that one consistent source of complaints among obstetric patients was the rotation of obstetricians whom a patient was likely to see during her prenatal visits; particularly annoying to some was the fact they could not count on their baby being delivered by their own physician.

In the same vein, women apparently prefer to have their routine outpatient gynecologic care provided by a physician with whom they have a long-term relationship. One study of the satisfaction levels of clinic versus private family planning care, while noting other differences such as waiting time, also noted that clinic users, who were generally more dissatisfied with their care, were more likely to be shuffled around to nurses, nurse practitioners, and counselors for parts of their visits, whereas the private patient could count on her private physician to provide most if not all services.[4] The one exception to this is the provision of contraceptive services to teenagers whose concern for confidentiality

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ABBREVIATIONS USED IN TEXT

IVF = in vitro fertilization
GIFT = gamete introfallopian transfer
ZIFT = zygote intrafallopian tansfer
HCFA = Health Care Financing Administration

overwhelms a desire to have services provided by a known and trusted professional, even though such confidentiality is likely to be respected under any circumstances.[5]

A 1986 study suggested that breadth and quality of coverage and cost are among the most important factors for consumers selecting health care coverage.[6] A 1990 study of new employees selecting among health care plans noted that freedom of physician choice, cost considerations, and the convenience of having all services available at a single location were the predominant factors in employees' selection of a managed-care plan.[7]

Although these two studies did not address specific clinical services, the study of new employees did consider availability of prevention and wellness programs, a category that might include contraception and family planning. This attribute, however, was rated one of the least important considered by new employees in selecting a health plan.

Another recent study on how consumers choose health insurance found similar attributes to be the most important: the extent of coverage for hospital stays; choice of physicians; cost of the policy; choice of hospitals; and a new service-specific addition, dental coverage.[8] No other clinically specific services were noted. Preventive programs, which would likely encompass contraception and family planning, were determined to be relatively unimportant.

Telephone interviews with marketing managers of managed-care organizations around the country reaffirmed the findings of these studies regarding the factors most likely to affect consumer choice of health plan. Employers are looking for the most comprehensive plan at the least cost. No specific set of services, including those for reproductive health, appeared to make a health plan distinctly more marketable. Rather, employers looked for the most complete package of services available.

Most of the managers also noted that employers must be targeted with marketing programs concurrent with or even before employees. According to these managers, employers, like employees, are most concerned with comprehensive coverage, cost, and choice of physicians. Moreover, some of these managers indicated that employers are their real market, with employees being secondary because an employee cannot sign up for a health plan that the employer does not carry.

Identifying Meaningful Differences

To the extent that a managed-care organization can claim to be different from other managed-care plans, it can presumably attract the segment of the market for whom that difference is meaningful and appealing. For example, some people may find the inclusion of a specific hospital to be an important component of a health plan, whereas others may view a low premium as being the overwhelming attribute that makes a specific health plan appealing.

In addition, although many differences exist between health plans, all differences are not necessarily meaningful. The explanation for this lies in the realm of consumer behavior. One of the classic approaches to examining the ways in which organizations meaningfully differentiate themselves is by using importance-performance ratings.[9,10] This approach calls for consumers to rate the importance of each attribute of an organization and how well the organization performs with regard to that attribute.

A simple chart (Figure 1) shows how importance-performance ratings can be used. For example, although a managed-care organization may be rated well on having a large panel of physicians and on its childbirth preparation classes, only the large panel of physicians would provide a truly meaningful differentiation for the managed-care organization because the childbirth classes are viewed by consumers as relatively unimportant.

Likewise, an organization's cost and member newsletter may be rated poorly. Given the low importance rating of the member newsletter, however, it would not be worth much effort to try to improve it. Why waste resources on something that is unimportant to your market? Whereas substantially improving cost would help create another meaningful source of differentiation for the managed-care organization. Only attributes rated as important by the consumer have the potential to provide meaningful differences among managed-care organizations. As discussed above, extent of coverage, freedom of choice of physicians and hospitals, and cost are the factors rated by consumers as highly important.

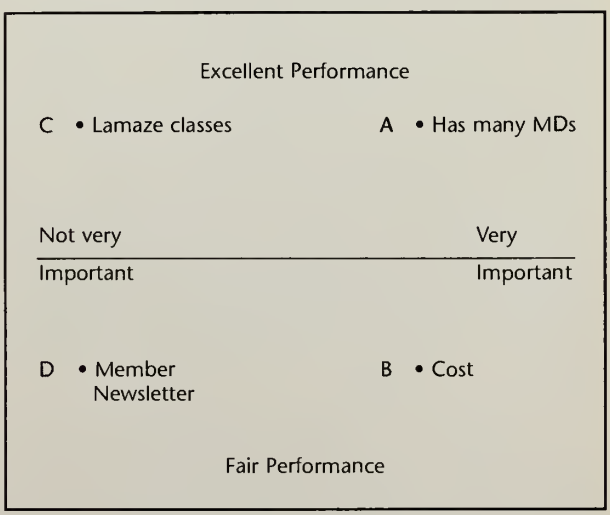

Figure 1.—Importance/performance ratings can be used to identify meaningful differences in health plans.

Some services can help cement a health plan's good image (assuming that it has one) but, by themselves, are unlikely to have an effect on customer choice because they are considered relatively unimportant. Services that are considered to be performed poorly may not be worth investing in for the same reason. The relevant question for reproductive health services, then, is this: Where do these services fall on the importance and performance ratings?

A second question relates to performance and competition. Assuming that reproductive health services are important enough in the consumer's or employer's mind to provide meaningful differentiation, does a specific managed-care organization do them so much better than competing health plans that there truly are meaningful differences? Not only must an attribute be meaningful to the consumer, but it must not be provided equally well by all competitors. If large numbers of competitors provide the same level of an attribute, it is not a differentiating factor. Therefore, one must ask: Are reproductive health services provided and covered equally well by all managed-care organizations?

Applying the Consumer Behavior Models

To carry the concept of a meaningful differentiator further requires the use of consumer behavior models. Such models are well established in the field of marketing, having been introduced more than 20 years ago.[11] They have also been more recently applied in the health care field.[10,12]

The consumer behavior models presented here analyze consumer purchasing decisions in terms of consumers' need for information combined with their perception of availability of information that could differentiate between the alternative purchase options. Three models of consumer behavior based on these two factors are generally identified (Table 1).

The low-involvement buyer perceives little risk to the purchase and sees it as a relatively simple decision; therefore, the buyer gathers little information. The decision not to gather information on the purchase alternatives is reinforced by the perception that no meaningful differences exist between them; therefore, additional information on the purchase alternatives would serve no useful purpose. A lack-of-information cycle then begins: Because the consumer sees no use in collecting additional information, the consumer cannot become better educated about any real differences that may exist. Further, if consumers see little risk in the purchase, they have little incentive to collect and analyze information regarding a decision for which all purchase alternatives are seen as approximately equal.

In the health care arena, examples of low-involvement consumer behavior involve preventive and early disease detection services. A consumer who has no history of hypertension but who believes that periodic blood pressure checks are wise would probably go to the most convenient location to get a blood pressure reading. This could be the local drug store, a health fair at a local hospital or managed-care organization, or the office of the consumer's physician at the time of a regular appointment. To the consumer, these may all be the same, as long as all of these alternatives are believed to provide a competent blood pressure reading.

TABLE 1.—*Three Models of Consumer Purchasing Behavior*

Purchase Criterion	*Low-Involvement Model*	*Learning Model*	*Dissonance Attribution Model*
Need for information.....	Low	High	High
Perceived availability of information	Low	High	Low

Most people believe they act by the learning model most of the time, although this is contrary to reality in many cases. In this model, buyers perceive a high risk to the purchase decision. This gives them the incentive to collect and analyze information on which to form attitudes about the purchase alternatives and then to buy based on these clearly defined attitudes. The learning model assumes that the available information allows the buyer to differentiate meaningfully between purchase alternatives. The buyer also enters the purchase process assuming that meaningful differences exist between purchase options and that the information available will clarify the distinctions between the alternatives.

The learning model of consumer behavior is found more often in the employer's health benefits office than in consumer buying situations. Because it is the duty of health benefits officers to gather information about health care providers and insurers, and because they are able to demand information from these same groups, they have an incentive to collect information about health care purchase alternatives. They also are more likely than the average consumer to have access to the type of information that would allow for meaningful distinctions between purchase alternatives.

Consumers do at times operate by the learning model, particularly as useful information becomes available to them. Patients with long-term health problems sometimes become avid readers about their problems and become sufficiently knowledgeable to act according to the learning model. Obstetric patients have occasionally achieved some notoriety because of their activism in obtaining data regarding hospital obstetric units, calling to determine if the hospital has birthing beds, birthing chairs, required episiotomies, epidural anesthesia 24 hours a day, and jacuzzis to help ease the pain of labor. Patients manifesting such an aggressive level of information search can usually be assumed to be acting by the learning model.

The dissonance attribution model also presents the buyer with a perception of high risk associated with the purchase and with the belief that meaningful differences exist between the purchase alternatives. Because of a perceived lack of available information that would allow the buyer to distinguish between those

alternatives, however, the buyer faces the prospect of making an important purchase decision with inadequate information.

Under these circumstances, the purchaser's decision often is to select the purchase option that appears to be the safest choice. The perception of safety can emanate from the purchase option having the most familiar institutional or brand name; from the recommendation of a friend or relative, who may have knowledge of only one option and therefore cannot adequately inform the buyer of the full range of purchase choices; or from any source that implies that one alternative is better than the others without providing sufficient information about the other alternatives.

Examples of dissonance attribution behavior can be found throughout the health care system. The selection of a physician seems most often to fall into the dissonance attribution model, not because the decision is viewed as unimportant, but rather because little information is available to allow the consumer to distinguish between available physicians.

The choice of a health insurance plan often is characterized by dissonance attribution behavior as well. In this case, however, although substantial information is available on the health insurance plans under consideration, much of that information is either intellectually inaccessible to the average consumer or so voluminous that the buyer is unwilling to do the work necessary to make use of the information. Again, the buyer resorts to making the safest or easiest choice.

Assael added a fourth consumer behavior model, in which the buyer exhibits low involvement but sees important differences between the alternatives.[14] This model, the variety-seeking buying behavior, does not appear common in health care purchase decisions.

Family Planning and Contraception

The literature and interviews with marketers of managed care plans around the country suggest that family planning and reversible contraception are viewed by consumers and especially by employers as a low-involvement service. Preventive services are rated as fairly unimportant in studies of how consumers select health care plans; many would characterize family planning and contraception as preventive services.

To qualify as low-involvement, a service must be viewed as being performed equally well by all available providers. Although those who provide the services might disagree and identify differences that are apparent to them as experts, the average consumer is likely to assume that physical examinations, contraception, and counseling can be provided equally well under any health plan. In addition, family planning and contraception are likely to be viewed as low risk, aside from the fear of loss of confidentiality, noted earlier as a concern of teenagers. Contraceptive methods provided by physicians are generally viewed as being quite effective if used properly, reducing their use to a low-risk situation. Unlike other services provided by a managed-care plan such as cardiology, oncology, and general medicine, which are required for the diagnosis and treatment of diseases that may be life threatening, contraception and family planning are viewed as low-risk services.

Under conditions of low involvement, where meaningful differences among the providers of a service or the risk of poor performance of the service is not apparent to the consumer, services such as contraception and family planning are not likely to weigh heavily in a consumer's choice of health plan. For example, a marketing representative from HMO Arizona, which does not cover any forms of reversible contraception, noted that, because competing managed care organizations do cover a range of contraceptive services, beneficiaries sometimes ask about family planning coverage. HMO Arizona's experience had shown that the lack of coverage of these services does not affect health plan choice, however, because the cost and comprehensiveness of coverage of other services outweigh the lack of coverage of family planning and contraceptive services.

The variability of coverage of these services, ranging from only 17% of preferred provider organizations covering diaphragm devices to 86% of HMOs covering intrauterine device insertion,[15] could lead to the assumption of a meaningful differentiation between health plans on the basis of reversible contraceptive coverage. If family planning and contraception are viewed as low-involvement services combined with a variety of higher involvement and high-risk services, however, the variability of reversible contraceptive coverage may not play an important role in selecting a health plan.

The same decision-making process appears to characterize employers' purchase decisions; as noted earlier, these decisions usually are based on cost, comprehensiveness, and range of physician choice.

Within the context of family planning and contraceptive service, high involvement would appear to rest primarily in the physician-patient relationship, rather than in specific services provided by a physician. This relationship extends beyond family planning and contraceptive services to include routine gynecologic and obstetric care, oncology, and other related services. Managed-care organizations vary in their coverage of routine gynecologic care, from 64% of preferred provider organizations covering annual gynecologic examinations to 100% of HMOs covering Pap tests.[15] In some managed care organizations, this high-involvement relationship may revolve around services that are generally not covered by the health plan, leading women to maintain this relationship outside of the managed-care plan.

Induced Abortion

Although little has been written in the health marketing literature on family planning and contraceptive services in general, even less is available on abortion. A reasonable marketing analysis explains this lack of emphasis, however. At the time that an abortion is need-

ed, it is viewed by the woman as a high-involvement decision but also a crisis-motivated purchase. It is a time-limited choice—a woman has limited time to gather information, usually only from the onset of the purchase process (when the woman begins to consider an abortion) to the time of the purchase (the abortion itself). In addition, little word-of-mouth information or shared knowledge about abortion is available, in part because of the disapproval that the decision elicits from many people. This suggests that women act according to the dissonance attribution model (high involvement, low perceived differences between alternative providers) when seeking an abortion.

It seems likely that most women who need an abortion will consult their managed-care provider, assuming that their health plan covers abortions. This is both the easiest purchase and, to the extent that the health plan's services are deemed trustworthy, the safest purchase, the mode by which dissonance attribution buyers act. If the woman's managed-care health plan is one of the 17% to 33% that do not cover abortion,[15] then the dissonance attribution model suggests that the woman is likely to take the recommendation of the clinician with whom she deals on a regular basis or to rely on whatever other recommendations she can find regarding which physician she should see.

Although abortion is viewed as a high-involvement purchase at the time it is needed, that time is unlikely to coincide with the purchase cycle for selecting a managed care plan. If consumers do not anticipate this particular purchase, they will view abortion as a low-involvement service when they select a managed care plan.

Even if it is viewed as a high-involvement service because the woman knows that she engages in risky behavior, she is still unlikely to be knowledgeable about differences among alternative managed care organizations' abortion services unless she is already aware of important differences among the abortion services provided, the quality of those services, and the extent of abortion coverage, all of which suggest a high use of these services from multiple providers. Interviews with managed care marketing managers support this conclusion and suggest that, in sales meetings with employees, few questions are raised with managed care organizations' sales representatives regarding abortion, given the sensitive nature of the service. Moreover, one respondent reported that, although abortion is covered by the HMO, that information is not reported anywhere in the organization's literature, including in the benefit listings, because they do not want anti-abortion forces knowing that they cover abortions. Therefore, from a marketing perspective, the use of abortion service coverage as a marketing vehicle is not a viable option.

Maternity

Unlike abortion, which most women do not plan in advance to utilize, maternity is one of the few in-patient procedures that consumers may anticipate well in advance of enrolling in a health plan. In addition, birth, unlike abortion, does not require a crisis-motivated use of services. In extreme cases, women have nine months to select the hospital in which to give birth; in reality, many will have less time to make their hospital choice because they wish to receive prenatal care from the same provider who will deliver their baby. This still places them well beyond a crisis mode, however. This period of time is even longer for consumers who are anticipating pregnancy but are not yet pregnant. As noted earlier, certain segments of the obstetric population engage in aggressive information searches regarding both prospective obstetricians and hospital maternity departments. Moreover, much word-of-mouth information is available about maternity services. Women (and sometimes the men who accompany them through the birthing process) often talk extensively in social and work settings about their birth experiences, unlike abortion, which few people discuss in public.

Part of this behavior derives from the fact that this is one of the few hospital stays in which the patient is usually healthy. The consumerism movement of the 1970s and 1980s has translated itself, in the obstetric setting, into a desire to reduce the medical aspect of the birth experience and empower the consumer to make choices previously reserved for the physician. The increasing amount of available information results in a substantial proportion of obstetric patients who are able to differentiate effectively between hospital maternity units.

Like any hospital stay, childbirth is a high-involvement experience. Pain or the prospect of pain evokes an intensely personal response, and, according to participants in many focus group interviews, what some natural childbirth teachers refer to as discomfort is, for many women, excruciating pain. Moreover, the risk exists that complications may develop at the birth; for those who are aware of these possibilities, the level of perceived risk is even higher.

The anticipation of pregnancy, the high level of desired information, and the intense level of personal involvement suggest that many prospective obstetric consumers operate by the learning model and that they do so far enough in advance of the birth that this learning affects the selection of their health plan. Maternity services, therefore, more likely than the services discussed previously, may be viewed as a meaningful criterion in the selection of a managed care plan, because the consumer may be looking for a specific obstetrician or hospital to be covered by the health plan. Even when the consumer has not undertaken an information search and has relied primarily on the recommendation of a physician, relative, or friend, that is, when the consumer is operating by the dissonance attribution model, she still has a high level of involvement and advance warning of the purchase of maternity services. Therefore, for the dissonance attribution consumer as well, maternity services are likely to be viewed as important and to affect the choice of health plan.

Hospitals recognize that obstetric care is a marketable service. In addition to its advance-warning status, women often select a physician based on hospital affiliation, rather than selecting the physician first.[10-16] Also, as hospitals began to compete for patients in the 1970s, they became aware that, if the woman gave birth at a specific hospital, she, along with her family members, was likely to return there for other hospital stays.

> Birthing centers have become the focus of many hospital marketing programs. Generalized obstetric services are often used as 'loss leaders' (services priced below their actual costs) in the hope that they will build hospital popularity and attract more profitable services in the future. . . . In the past, most patients looked to their physicians for guidance in selecting a hospital obstetric service. More recent thought is that women themselves are becoming the key decision makers in this selection process.[16(p 71)]

In addition, if positive birth experiences at a hospital lead to a positive word-of-mouth reputation in a community, the hospital may be able to compete more effectively for managed care contracts.[17]

Most obstetric marketing efforts have been undertaken by hospitals rather than managed care organizations. Most births take place in hospitals; therefore, because the birth is probably the most momentous event in a woman's reproductive life, women consider the selection of a hospital when choosing a health plan. Most women think of the birth experience in the context of the hospital, not the specific HMO. In addition, a managed care plan that permits obstetric service at more than one hospital would have difficulty making specific statements about its obstetric service because that service could vary from hospital to hospital.

Infertility

Couples with established or suspected infertility weigh a health plan's infertility services heavily in their choice of a health plan. The perceived risks involved with infertility and the services designed to address it are high. The effects of infertility are felt in areas ranging from life-style and self-esteem to social interaction and emotional well-being. The painful question associated with infertility—What if I can't have a baby?—places this in the realm of truly high-involvement services. In addition, the costs of the more high-technology services are high, and the coverage is limited. Only 16% to 17% of managed care organizations cover in vitro fertilization (IVF). Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT), which cost on average $6,200 per cycle (S. Caminiti, "The Ordeal of Infertility." *Fortune*, August 8, 1994, pp 98-103), are even less likely to be covered because the Health Care Financing Administration (HCFA) has determined that these procedures are unusual, infrequently provided, and not necessary for the protection of individual health (58 Federal Register 51632, October 4, 1993). This determination permits federally qualified health maintenance organizations to exclude these services from the basic health services they must provide to their members.

Many patients being treated for infertility engage in aggressive information searches because, like obstetric patients, they are not in a crisis mode. In addition, much information has been made available to infertile couples regarding how to shop for infertility specialists. Since 1989, the American Fertility Society has been publishing the success rates of fertility service programs that do high-technology procedures (IVF, GIFT, and ZIFT), and numerous articles and books have been published on the subject. Therefore, a couple who are so inclined can engage in a successful information search and act by the learning model.

Other infertile couples may be limited to a particular physician or infertility service, either out of desperation or because only one such program is available within commuting distance. These couples are acting by the dissonance attribution model.

Between 7% and 9% of all couples of childbearing age experience impaired fertility, and this represents a significant segment of the market to which managed care organizations might market themselves. Like women of childbearing age, infertile couples are also anticipating pregnancy, but with greater uncertainty and an increased awareness of a health plan's capability to offer infertility specialists, willingness to pay for tubal ligation or other infertility-related surgery, high-technology procedures, and infertility drugs.

Given the high level of involvement, the coverage of infertility services can make a managed care plan more marketable to these consumers. Admittedly, infertile patients present the probability of costing a managed care plan more if they request in vitro fertilization, surgical procedures, and other expensive treatments, making them a financially less attractive segment of the health care market. Therefore, although managed care plans could easily offer meaningful differences to consumers in the area of infertility, they might not wish to do so for financial reasons.

Conclusions

The factors affecting the choice of a managed care plan are those that are high-involvement issues, ones that employers and employees or consumers view as important. Given the total range of services and considerations that the selection of a health plan raises, and given the findings of research into health plan selection that stresses the importance of a plan's cost, comprehensiveness, and choice of physicians and hospitals, it is unlikely that family planning, reversible contraceptive services, or abortion will have a serious effect on the selection of a managed care plan.

Although women's health became a key topic among marketers in the 1980s and has remained so through the mid-1990s, these marketing efforts have been focused primarily on obstetrics, the high-involvement service that can be differentiated in advance to the customer. As the baby boom generation has moved into menopause, services related to this area have also become a marketing focus, for the same reason. Lower involvement areas

of women's health, although expected to be included in a package of women's health services, are not major attractions for women consumers.

This in no way suggests that reproductive health services in themselves are unimportant. If birth control pills worked only occasionally, intrauterine device insertion resulted in a notable number of deaths, and so on, then the risk of these services would rise and they would become high-involvement services. Under these conditions, managed care organizations that provided reliable and competent reproductive health services could effectively differentiate themselves from the competition.

In the current market, however, family planning, contraception, and abortion services are viewed, based on routinely good provision of these services, as safe commodities, needed services that can be performed well by any managed care organization. Therefore, they are not viable points of differentiation for marketing managed care organizations.

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Women's Reproductive Health

A Catholic Perspective

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In the minds of many, Catholic health care institutions and women's reproductive health go together in very limited ways. Those limits are probably captured fairly accurately in such phrases as "Catholic hospitals refuse to do abortions," or "in vitro fertilization is against church teaching." A fuller Catholic perspective on women's reproductive health, however, may have less to do with prohibited procedures and more to do with health. I propose that women's reproductive health goes beyond certain controversial procedures. I suggest that the Catholic perspective on women's reproductive health takes place in a broader context, the context of the changes in the health care delivery system in which integrated delivery networks, collaboration with non-Catholic partners, and managed care play a large role.

In this context, the concept bears repeating that reproductive health is directly related to overall health. For example, fertility is affected by sexually transmitted diseases, healthy childbearing is affected by nutritional status, prevention and detection of reproductive cancers are affected by early intervention. In addition, in the United States, women's access to health care, both preventive and acute, is limited by their employment status, their financial resources, their geographic location, and their social status.

If we understand women's reproductive health as more than their capacity to limit their fertility,[1] then the first ethical issue to be addressed should be justice. Women (and men) should be guaranteed basic health care, which, in the Catholic moral tradition, is their right.[2,3] The US bishops write, "Health care is so important for full human dignity and so necessary for the proper development of life that it is a fundamental right of every human being (US Catholic conference on health and health care, Washington, DC, 1982, p 5)." Catholic theologians, ethicists, and pastoral leaders also have written widely about health care as a right.

At least in the past several years, Catholic health systems, that is, collections of Catholic and non-Catholic hospitals that are organized to provide service over a large geographic area and share central services, have acted on this belief. High on the agendas of these health care organizations are changes in the national health system that would move toward universal insurance coverage and universal access to basic health care. Some of these organizations have full-time employees in system-level advocacy positions whose job is to encourage government, industry, and financial institutions to enact changes in the social structures that now keep people poor, unemployed, and uninsured. Among those Catholic systems in California that have full-time positions in advocacy are Catholic Healthcare West in San Francisco and St Joseph's Health System in Orange. The changes that these Catholic providers are seeking will no doubt benefit women's reproductive health as well as their general health because they will improve the ability of poor people to get health care, and more women than men are poor.

In the wider context of health care in the United States, then, the view of Catholic health care changes somewhat from a focus on forbidden procedures to one of appropriate, comprehensive care for all members of society. In the vacuum left by the federal government's ill-fated attempt at health care reform, Catholic hospitals and systems, like other players in the health care market, are making their own contributions to reforming the system. In California, these changes are resulting in a market that is increasingly serviced by managed care.

For Catholic hospitals and systems, this means collaborating with physician groups, payors, and providers of services that are necessary within managed care networks but are not necessarily within the expertise or the geographic reach of the Catholic system. In some cases, this has meant the purchase and management of physicians' office practices; in others, it may mean a merger or affiliation with a hospital or provider that is not identified within the community as Catholic. In other cases, a hospital may be willing to enter into a full affiliation with a Catholic provider, but has been providing services such as sterilization to the community and is not willing to discontinue that service. In discussions with the local bishop, who has ultimate ecclesial responsibility for the Catholic identity of a given facility in his diocese, these trade-offs are worked out to the satisfaction of the new partner, the Catholic facility, and the community that is being served.

Some clarification is appropriate here about the difference between the provision of contraception services (including sterilization) and abortion. In official Catholic teaching, abortion is understood to be the taking

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From Catholic Healthcare West, San Francisco, California.
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of innocent life and, as such, is never morally acceptable. The moral gravity of abortion and of contraception are seen as different issues by the Catholic Church and are therefore treated differently in the negotiations that are part of structuring affiliations with physicians, with payors, and with other providers in the community. Catholic facilities do not promote contraception, but the Catholic sponsorship of a physician office practice does not mean that no physician in it can discuss or prescribe contraceptives. That issue involves the confidentiality of the physician-patient relationship, which Catholic sponsors respect. Because providing some of these services is a condition of continuing the more important overall mission of Catholic health care, Catholic facilities and compassionate bishops have often been willing to tolerate the provision of contraceptive services, especially in view of the fact that the official Church leadership's view of the immorality of contraception is not widely held by either Catholics or society at large.

Abortion services are another matter entirely. The American public, including the American Catholic public, is divided on the issue of abortion. Some think the evil of taking innocent life is always wrong; others believe it is always tragic but not always the least moral choice. The controversy over gag rules, parental consent, spousal consent, Medicaid funding, waiting periods, and the inclusion of abortion in a basic benefit package are all indicative of the deeply unsettled nature of the position of abortion in our national moral conscience. Even physicians are divided. Whereas most physicians think second-trimester abortions should be available to women, very few of them are willing to do those procedures themselves.[4]

Whatever one thinks of the Church's stand against abortion then, that stand is not drastically at odds with where we are as a society. Along with euthanasia, abortion is a deal breaker in a possible merger or affiliation; straightforward elective abortion is so contrary to the fundamental nature of Catholic health care that it can never be a point of compromise. Interestingly, it is rarely necessary to forego an affiliation because of abortion—most abortions in this country are not done in hospitals, and hospitals that have provided those services have been willing to give them up when seeking to merge with a Catholic entity. Furthermore, the stereotypical notion of the antiabortion stance of the Cathoic Church is not necessarily an accurate reflection of that stance. Terminations of pregnancy that are the indirect result of an attempt to save the life of the mother are permitted in most Catholic hospitals. In fully integrated delivery networks, however, in which a comprehensive array of services is made available to a specific population by a range of different providers, not all the service providers will be Catholic or even formally affiliated with Catholic entities. As these networks are formed, with payors and with other service providers, Catholic health care leaders will be challenged to find ways to cooperate that compromise neither deeply held moral beliefs nor the ability to continue serving the health needs of their communities.

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Women's Health Care in an IPA Setting

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Tremendous changes are occurring in the health insurance industry today, mostly in response to consumer demands for the maximum coverage they can obtain while still keeping costs low and quality high. This has led to a proliferation of plans of various types. These range from the traditional indemnity plans to the health maintenance organization (HMO) concept of requiring all tests and procedures to be approved by a primary physician to "point of service" plans, wherein an individual or group can use the services of any physician or hospital in or out of their basic HMO system by agreeing to pay a higher premium and co-payment for office visits, surgical procedures, and hospital stays that they utilize outside the system.

US Healthcare operates an independent practitioner association (IPA)-model health maintenance organization that provides access to medical care in eight states in the Northeast and Middle Atlantic regions. It also operates in Washington, DC, Georgia, and, in the near future, in Virginia and North and South Carolina. Almost 1,800,000 members are served by an independent network of 8,000 primary care providers and 25,000 specialists, including 3,300 obstetrician-gynecologists. All physicians must meet specific criteria to participate in the network. For example, all specialists must be board-certified within five years of completion of their residency or fellowship, a standard that the company thinks is essential in assuring a high quality of service for its members. Recertification of primary physician providers by the company is required every year, allowing close review of each physician's medical activities.

US Healthcare prides itself in generating innovative health care, especially in the use of individual case management. It was among the first HMOs to develop "report cards" for primary physicians (and later for obstetrician-gynecologists) based on quality of care, quality of service, efficiency of care, and patient satisfaction. This responded to members' desires for a method of evaluating their medical care in an HMO setting.

The company identifies strengths and weaknesses through surveys of its members and communication with providers. As a result of this process the company instituted a direct access visit for female members so that they might see their gynecologist for an annual breast and gynecologic examination without prior written referral. Also, any office procedures necessary for diagnosis or treatment of a gynecologic disorder can now be done at the time of a member's visit without additional referrals and return visits.

One source of discontent among gynecologists has been the company policy of allowing only primary physicians to order radiology studies, including mammography. In 1995, US Healthcare intends to allow gynecologists to issue referrals for mammograms, provided that a copy of the procedure report is sent to the primary physician, who remains responsible for the overall management of women's health care needs. Direct referral by the gynecologist is intended to facilitate gynecologic care for the member.

Another area of change involves a new infertility program featuring a two-tiered level of infertility management aimed at decreasing repeat surgical procedures. When a diagnosis of infertility is first made, a woman continues seeing her own obstetrician-gynecologist or primary physician for basic evaluation and treatment, exclusive of surgery, through four cycles of clomiphene citrate, if indicated. At that point, if a member has not yet conceived or if a surgical procedure is needed, she will be referred to a participating infertility specialist. Participating providers are approved on the basis of their ability to provide all services up to and including advanced reproductive technology. All of the above services may require a small co-payment fee by the member amounting to less than $20.

An IPA-model HMO, with a discrete population group such as those operated by US Healthcare, has a capacity to gather a tremendous amount of data and thereby compare its outcome results to national norms to determine its strengths and weaknesses. For instance, Health Plan Employer Data and Information Set 2.0 (HEDIS 2.0) data show that 70.9% of US Healthcare women members over age 50 had mammograms compared to a Healthy People 2000 goal of 60% for that population. The Healthy People 2000 goal for women receiving pap smears in a three-year period is 85%; US Healthcare had a 73.6% rate, indicating room for improvement. As a result, we are starting a program aimed at increasing the number of women who go to their physician for a gynecologic examination and pap smear and creating a system to contact those women with abnormal results to assure proper management.

HEDIS 2.0 data reveal that only 84.3% of US Healthcare's pregnant members came for care in the first trimester compared to the Healthy People 2000 goal of

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90%. We hope to improve our percentage by educating women members via mailings on the importance of early prenatal visits. The incidence of low-birth-weight infants weighing less than 1,500 grams in US Healthcare members was only 0.84%, lower than Healthy People 2000's goal of 1%; our incidence of infants weighing less than 2,500 grams was only 4%, while Healthy People's goal was 5%. Although other factors certainly are involved, these results may be attributable to early case management.

The US Healthcare Check mammography program is another example of a program managed with close follow-up. Every woman member aged 40 to 50 years is contacted by mail to get a mammogram every one to two years, based on risk factors identified in member surveys. After age 50, members are notified annually to get mammograms. Those with abnormal study results are contacted to be sure there is appropriate medical follow-up. This program was instituted several years ago as a result of a delay in response time to abnormal mammograms. The radiology facility had not been contacting members or physicians in a reasonable length of time, thereby delaying further evaluation and treatment, if needed. With the current program this problem has lessened, with all concerned parties being promptly notified of abnormalities.

US Healthcare also has a special program for high-risk pregnancies—the "L'il Appleseed" program. A single phone call to an 800 number puts a member, or the primary physician or obstetrician in touch with a high-risk nurse manager who facilitates referrals, admissions, and tests that the member needs. This eliminates the need for multiple phone calls for referrals previously required during the course of a complicated pregnancy.

The determination of "high risk" is based on criteria set by the US Healthcare Perinatal Committee and the OB-GYN Quality Assessment Committee. A member is determined to be at "high risk" from a questionnaire sent at the time of prenatal registration or as a result of complications occurring later in a pregnancy. US Healthcare recommends that any patient with "high risk" potential see a perinatologist at least once during her pregnancy, for evaluation and management, despite the high cost associated with such visits. Our goal is to decrease perinatal morbidity and mortality. Whether the perinatal evaluation helps in this regard remains to be seen, but data are currently being gathered on this issue, and this could be a factor in the low rates of low-birth-weight children previously noted.

Quality Assurance Committees have now been established for most specialties. These committees meet regularly to evaluate medical policies and procedures within their specialty and set standards for US Healthcare participants.

Finally, another great change is occurring today as managed care companies service Medicaid recipients' medical needs. This creates a unique challenge for US Healthcare. The US Healthcare Family Care Plan developed for Medicaid families attempts to be seamless. It is set up so that there is no differentiation between the care given a woman who is on Medicaid and a woman who is not. Both receive US Healthcare cards and select a primary physician and gynecologist for services. Family Care Plan members are eligible for all the benefits of other US Healthcare members, but may need to learn how to use a system in which they have their own primary physician, rather than an emergency department, tending to their medical needs.

The US Healthcare program has been presented as the paradigm of how an IPA can best function in delivering health care. Managed care is not only the wave of the future; it is here now, and it is here because it makes sense medically and economically. In this particular arena—women's health care—it offers a good method of providing access to high-quality care with the capability of getting large numbers of women to make more use of preventive and early diagnostic measures, thus promoting better overall health, disease prevention, and management. And it does this at a substantially lower cost to the public than traditional fee-for-service medicine.

THE HENRY J. KAISER FAMILY FOUNDATION

Integrating Essential Public Health Services and Managed Care

Family Planning and Reproductive Health as a Case Study

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Change is always hard. Even desirable change has disconcerting aspects; inevitably it is less linear and smooth, and less flawless, than at first envisioned. Small but thorny problems defy solution, and resolving them requires a disproportional share of the total time and effort available. Finding a satisfactory place for personal medical services with public health implications within the managed care transformation is exactly such a problem. Family planning and reproductive health care provide a clear example. They are essential services affecting population health status. The challenges encountered in integrating them within the managed care framework provide a good case study of dilemmas that remain to be solved.

Many issues must be faced by those who set public policy, by the purchasers of care, and by the providers of care, including some managed care organizations. They include:

- Distinguishing between preventive and therapeutic services so that management efforts to constrain utilization do not also constrain prevention;
- Identifying the costs of adverse health consequences that occur when preventive care is *not* provided;
- Organizing the delivery of services with sufficient intervention time to permit prevention education and counseling;
- Providing for confidentiality in the delivery of sensitive services; and
- Finding innovative ways to recognize and compensate a health plan for investment in prevention that results in long-term savings in the future, but may not produce savings in the immediate term while the patient is covered by that particular plan.

An important sector of the managed care industry has its roots in indemnity insurance. Their perspective naturally reflects their historical vision of health services as insurance risks for which actuarial calculations can be applied to determine a fair cost for providing indemnity. The overall goal in the risk-indemnity (insurance) model has been to spread the burden of cost for illness and injury intervention—intervention that all participants in the system, with the possible exception of care providers, would hope could be avoided or minimized. Approaching managed care from this perspective, the first impulse in attempting to control cost is to reduce the amount of intervention—to reduce the amount of care dispensed by the system. Preventive health care services, on the other hand, are services that all participants in the system, plan owners and policy makers, plan managers, care providers, and care recipients, should want to maximize. Thus the first impulse in this case would be inappropriate. Measures designed to reduce care utilization, such as gatekeepers and authorization procedures, may well act at cross-purposes in the provision of preventive services because the goal is opposite.

In the case of prevention, plan members may need to be lured, at the very least encouraged, to seek care; services must be readily accessible, with all barriers minimized. So in setting policies for managed care, it will be crucial to distinguish at least two distinct and opposite service categories: services that all should hope to avoid and minimize (illness and injury services); and, services that all should hope to utilize fully and liberally (preventive services). So far, managed care has had notable success in dealing with the first category. The second category, on the other hand, is not yet uniformly recognized, and effective translation into policy remains to be fully developed.

It may seem odd to start with costs, but today's discussion about health care delivery focuses on it. The first accounting systems in managed health care were designed to capture costs associated with provision of services and to control utilization. Some of these are costs that accrue in treating an adverse outcome. These costs also need to be identified and incorporated into accounting methodology. Modern systems increasingly take into account the need to decrease utilization of particular services and increase the use of others. Family planning and reproductive health care services are an especially good case study because the cost-effective-

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ness value of these preventive services is immediate and large. Unintended pregnancies and complications of sexually transmitted infections are costly, and both incur immediate medical care costs within the 12- to 18-month time horizon that plan managers use now for cost projections.[1] There can be no doubt that cost-effective interventions to prevent unintended pregnancy or infection complications will save a plan money. Failure to deal effectively with these issues is illogical and would indicate that cost information is either not always appropriately tabulated or that its implications are not being logically applied.

What are the obstacles now in some managed care settings that may be impeding effective family planning and reproductive health services? Three major problems are providing sufficient time for education and behavior-changing intervention, providing barrier-free access to caregivers with the knowledge and skills necessary to provide comprehensive family planning and reproductive health care, and providing confidentiality protection.

The gatekeeper format, intended to insure appropriate care and care continuity, means that access to the care-giving system is channeled through a single gatekeeper, usually a primary care clinician. Because the supply of primary care clinicians is constrained in most geographic areas and financial pressures are substantial in most plans, primary care providers are almost certain to have busy schedules. They may be expected to see as many as 40 patients a day. Providing family planning and reproductive health care is probably within their scope of practice, but is it realistic? A ten-minute patient visit does not permit sufficient time for the education and counseling needed. It may be enough time to dispense a prescription for birth control pills, but it is not enough time to have a meaningful discussion of other options or to foster wise decision-making or the optimal use of any method.

Also, the primary care clinician may not have sufficient expertise in family planning or reproductive health care to provide, on-the-spot, a full range of contraceptive options. Training and experience with providing emergency contraceptive pill treatment after unprotected intercourse,[2] IUD insertion,[3] or use of contraceptive implants, for example, are limited in most communities. If a gatekeeper is not comfortable with or qualified to initiate these options, how likely are they to be recommended, to be described fully, or have their advantages presented in an appealing way? It is human nature to shy away from the unfamiliar and to avoid the need to acknowledge any lack in skills. And at the very least, a second care visit would be necessary for anyone who chose one of these options. These problems are especially tragic barriers because they bias contraceptive choice against some of the most efficacious and cost-effective method options available.[4]

On the surface, protection of confidentiality seems to be a simple problem to solve. Managed care success, however, is intimately linked to the full exploitation of powerful management information systems. Detailed care service information is necessary if plan managers are to play a role in insuring optimal utilization and quality assurance. How, then, can the identity and nature of certain services be kept confidential? If they are kept confidential, how can the quality of family planning and reproductive health be monitored, and how can coordinated and continuous care be assurred? This problem is further compounded by the increasing consolidation of health resources into larger and larger health care systems. Within such a system, dozens or even hundreds of care providers and their staff members are likely to have access to detailed patient care information including diagnosis codes. Finding solutions to this problem is imperative. Lack of confidence in confidentiality measures constitutes an insurmountable barrier for many who most urgently need such care.

Many essential public health services share the problems described above for family planning. In addition, a major problem for many preventive investments, including those in family planning and reproductive health care, is the short time horizon in which any single managed care provider can expect to realize a return on investment. Some health resources will benefit in future years from investment today in behavior intervention for smoking cessation or a healthier diet, or from excellent initial education in family planning. To make such investment attractive, however, mechanisms need to be devised that can allocate credit for the future benefit of this prevention investment. It may be possible to develop industry-wide prevention standards, with appropriate provisions for quality reporting, so that no plan would be penalized by its investment in prevention services.

Notwithstanding these daunting challenges, encouraging examples of change are underway within the managed care sector. Many plans now recommend and provide an annual "well-person" visit for risk-assessment and a physical examination. This visit is an opportunity for prevention education and for early intervention. The idea of outreach that proactively fosters care-seeking, however, is still foreign and is needed. Some plans have long had health education provided by specialized staff and other clinicians. Others are experimenting with new ways, including the use of audio-visual education tools. These education methods have been used widely in family planning clinics, and managed care providers would be well-advised to expropriate them wholesale and to look for new health education applications of more powerful and sophisticated information technologies.

Essential public health issues, especially family planning and reproductive health, have not received the emphasis they deserve in medical school and specialty training curricula. Historically, professional education has stressed curative (illness) care, despite the fact that preventive services like family planning represent such a large proportion of overall care needs.

Managed care organizations need to compensate for this problem. Existing primary care providers and health

personnel within managed care organizations need to be provided with additional training. Human resources can also be bolstered by adding already-trained personnel, recruited from the public health, family planning, and reproductive health care sectors, as single-focus health services are increasingly absorbed into larger health systems. In the future, managed care systems need to advocate for richer coverage of public health issues at all levels of professional education.

As in many undertakings, the attempt to integrate family planning and reproductive health care services into a managed care format reveals that the devil is in the details. And getting the details right may well determine the eventual success or failure of the endeavor. Similar problems also plague current efforts to find workable models for other essential public health services.

Meanwhile, existing care resources, such as community family planning clinics and public health clinics that treat sexually transmitted infections, need to be preserved until the details are solved and the services they provide are fully integrated into the emerging system. It would be a public health tragedy to allow even temporary disruption of these prevention services. In the case of family planning and reproductive health care, a prompt rise in pregnancy rates, with a parallel increase in unintended births and in abortion rates, and rising rates for sexually transmitted infection complications, would be the sad and costly consequences.

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